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Editorial

One Year Later

WITH THIS ISSUE the Journal completes its first year of publication. It has been an eventful and stimulating year. The Editorial Board and I believe that the Journal has filled a need in clinical cardiology and has successfully carried out the aims expressed prior to its publication by the Publications Committee of the American College of Cardiology.

As in all publishing media it is difficult to satisfy completely the needs and desires of all readers because of their different backgrounds, training, experience, and interests (for example, clinical vs. laboratory). Our announced aim was to dedicate this Journal to clinicians and to orient it toward clinical cardiology. We have maintained its scientific level as high as possible without allowing it to become too technical for the internist and cardiologist. The numerous enthusiastic comments received from our readers and contributors have led us to believe that we are accomplishing this purpose. Typical were such comments as "This Journal definitely fills the gap and is needed by the practicing cardiologist. Please keep it on a clinical and not a purely research level."

The rapidly growing list of subscribers and contributors to the Journal attests to its established success as a new medium for teaching. Surely the list of authors in Volumes I and II has been most impressive. It has been particularly gratifying to note the number of excellent contributions from the members of the College, including selected papers presented at the Annual and Interim Scientific Meetings. In this way the Journal has served to carry out one of the primary aims of the College, postgraduate education in the field of cardiology.

Our efforts to advance and disseminate clinical knowledge in a field which is rapidly becoming more and more complex will continue. We will maintain our policy of concentrating on clinical studies and reviews and frequent symposia and seminars, such as the one in this issue on atrial septal defects, in order to bring up to date the developments and problems in selected topics of current interest and importance. Other symposia planned for the coming year will be on phonocardiography, cardiac arrhythmias, diuretic therapy, peripheral vascular and cerebrovascular diseases, cardiovascular emergencies, ventricular septal defects, and aortic stenosis.

I wish to thank and express my appreciation to all those who have devoted their time and efforts and contributed to the rapid growth of the Journal. The Assistant Editor and the publishers and their editorial staff deserve no little credit for their devoted help and cooperation. Their efforts and zeal have helped to make this a "quality journal" in appearance, style, and readability.

All constructive criticism directed to me concerning the contents of the Journal will find an "open mind." I am exceedingly grateful to all who have taken time to write and send me their comments and suggestions. The warmth, sincerity, and friendliness of these personal notes have given me great encouragement to continue the many tasks required of an Editor. To all these old and new friends and associates, to all our readers and to all members of the College, I extend Seasons Greetings and best wishes for a Happy New Year.

SIMON DACK
Editor-in-Chief

Symposium on Atrial Septal Defect

Introduction

The following series of articles covers many of the problems of interatrial septal defects. In our series of 500 cases of congenital heart disease, interatrial septal defects were one of the most common malformations of the noncyanotic group. In comparison to other lesions of the noncyanotic group, interatrial septal defects give few physical findings. There is a more constant grade 1 or grade 2 systolic murmur over the base of the heart which is readily confused with a functional murmur. In many of our referred cases the diagnosis was first suggested by the appearance of an enlarged pulmonary artery with increased vascular markings of the lung fields found when the chest was x-rayed for some unrelated cause. Another chance finding has been the presence of an RSR′ complex in V_1 in the electrocardiogram, with or without other signs suggestive of right ventricular overloading.

The diagnosis is usually confirmed by cardiac catheterization. The appearance of increased O_2 content at the right auricular level is almost a constant finding. In many instances the catheter is passed to the left atrium through the defect. This is more easily accomplished when the catheter is threaded through the saphenous vein to the inferior vena cava and then to the right auricle, which allows for an easy exploration of the auricular septum.

Special technics such as dye dilution and selective angiocardiography have been of aid in the problem case with anomalous pulmonary venous drainage. Rapid strides have occurred in the treatment of interatrial septal defect. The blind technic for closure in our hands was only partially successful. In a review of our cases surgically treated by this technic, the defect was completely closed in only 65 per cent. Now in our clinic all interatrial septal defects are repaired by the open technic with complete closure, giving an extremely low mortality rate of 3 per cent.

We believe that any patient with an interatrial septal defect is a candidate for surgery by the open technic.

In the following articles the authors have discussed in an excellent manner the major aspects of interatrial septal defects, and I want to express my appreciation and thanks for their contributions to this issue.

Henry A. Zimmerman, M.D., F.A.C.C.
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Guest Editor

Atrial Septal Defects

A Clinicopathologic Appraisal*

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THE SURGICAL management of interatrial septal defects has become definitive with the employment of the heart-lung bypass and open cardiac technics. Clinical studies by x-ray examination, angiocardiography, electrocardiography and physiologic methods employing cardiac catheterization have led to highly accurate evaluation of anomalies before operation. In some cases, multiplicity of defects and/or unexpected vessel locations lead to findings of which the surgeon is unaware, until he has performed the cardiotomy. The purpose of this paper is to review various aspects of interatrial septal defects and to present the type of cases that we have encountered. Fortunately most interatrial septal defects occur in the region of the foramen ovale complex, and are easily closed in contrast to ones involving other sites. Shunting of blood through the defect from the left atrium to the right atrium with resultant increased pulmonary blood flow and right ventricular hypertrophy is the basic physiologic change. Repair in these cases is ordinarily followed by vast improvement in cardiopulmonary hemodynamics. The reconstruction of interatrial septal defects of persistent ostium primum, and especially of persistent common atrioventricular canal, on the other hand, offers problems of major magnitude.

EMBRYOLOGY

The complex patterns in the development of the heart from a simple tube to the dual circulatory pump provide many opportunities for derangements to occur. The acquirement of an interatrial septum is usually completed by the end of the seventh week. This begins as a separation of the single primitive auricle into two parts by a primary septum, arising as a sickle shaped partition, from the cephalic and dorsal wall. Gradually this elevates, until it meets with the atrioventricular cushions, which concomitantly have been dividing the atrioventricular canal into two parts. The final fusion of the limbs and the advancing edge of the primary interatrial septum to these cushions obliterates the diminishing passageway known as the interatrial foramen prism.

During the same period (the sixth–seventh embryologic weeks), a new opening in this septum is appearing in a previously intact site by a congeries of perforations, which coalesce to give rise to the foramen secundum. During the seventh week, the crescentic septum secundum develops to the right and parallel to the septum primum. This arises from the cephalic and dorsal wall of the auricle, but the bulk of its structure is more caudal than the initial septum. The caudal limb of the crescent fuses with the atrioventricular cushions just to the right of septum I. This fold ceases to grow after it has reached the point of developing an opening, the foramen ovale, which provides an oblique passageway in continuity with the foramen secundum. The overlapping portion of the septum I becomes the so-called valve or flap of the foramen ovale. Postnatally with establishment of respirations, a high left atrial pressure approximates these structures, so that there is cessation of the interatrial communication.

Concomitantly, during the period of provision of the interatrial septa, the auricles undergo changes whereby they become the atria. This is accomplished by incorporation of parts of the right sinus, and parts of the inferior and

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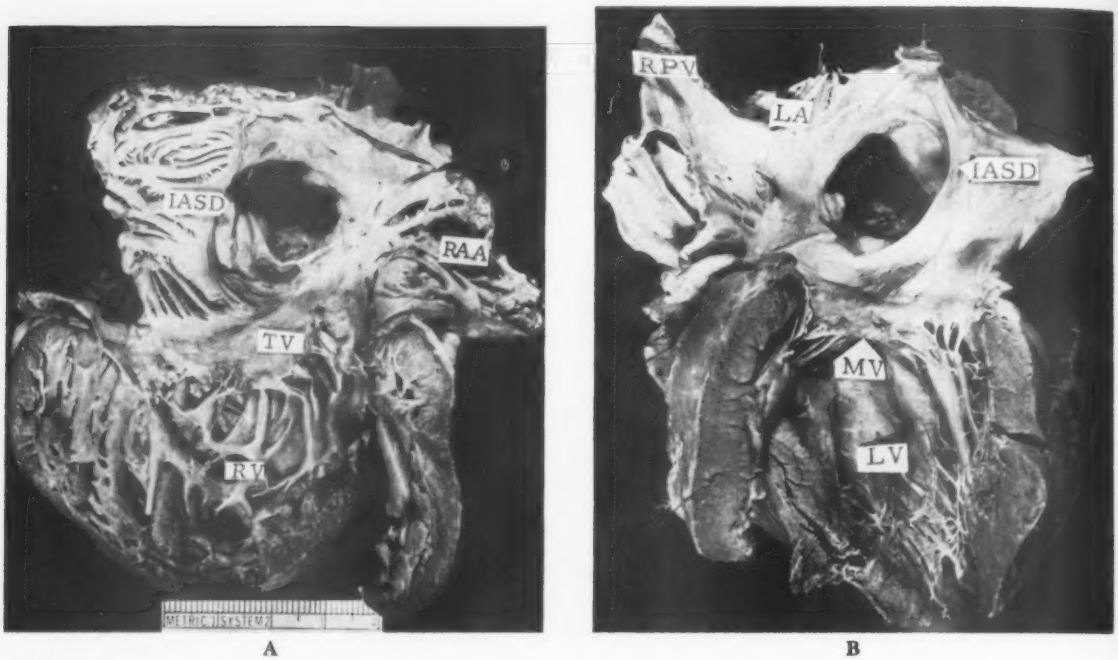


A B

Fig. 1. Large interatrial septal defect of foramen ovale complex. (A) View from right atrium; shows extensive underdevelopment of septum secundum. Filaments of endocardium traverse lower part of defect. IASD—interatrial septal defect; TV—tricuspid valve; RA—right atrium; RV—right ventricle. (B) View from left atrium; shows extensive opening of the septum primum which in conjunction with large foramen ovale provides a severe defect. RPV—right pulmonary vein; LA—left atrium; MR—mitral valve; LV—left ventricle.

superior venae cavae with the right auricle to become the right atrium; and by portions of the pulmonary veins and left auricle to become the left atrium. The bulk of the muscular portion of the interatrial septum develops from the interatrial septum II.

Anatomicophysiologic Considerations

The anatomic features of the atria and interatrial septum are discussed in detail in various textbooks. The description in Bailey's text[1] is of value particularly because of its surgical approach. The surgeon has often been handicapped in the past with closed technics in recognizing anatomic features by the small size of the surgical field and distortions of the heart by malformations. Direct visualization of the atrial chamber and septa has been greatly simplified with the use of open heart technics for the closure of atrial septal defects. However, landmarks which appear obvious in an autopsy specimen, may be difficult to evaluate readily during operation. Identification of the entrance of the venae cavae, pulmonary veins and of the coronary sinus, despite the presence or absence of disproportions in the size of the atria, aid materially in establishing the features from which the position of the atrial septum can be determined. In cases where an interatrial defect is present, and the foramen ovale complex is intact, recognition of the other type of defect is readily accomplished on the basis of its position. It follows naturally that accompanying anomalous positions of either the venae cavae, coronary sinus or the pulmonary veins have to be defined, in order to accomplish surgical correction.

The position of the conduction apparatus in atrial septal defect is ordinarily not altered, with the exception of foramen primum defects. In the latter, failure of complete formation of the central fibrous body leads to an abnormal posterior position of the atrioventricular node and bundle. A surgical procedure may, therefore, be altered during the course of placing sutures when there is abnormality of the conduction mechanism produced.

In isolated functioning interatrial septal

defects, the shunt of blood is from the left to the right atrium. The volume of the shunt is largely dependent upon the size of the defect, and is usually described as giving rise to pulmonary flows which are two to four times greater than the systemic flow. Transposed into figures, volumes in adults may be 10–16 *l*/min through the pulmonary circuit and 4 to 5 *l*/min in the systemic circulation. There may be a slight intermingling of venous with arterial blood by eddies entering the left atrium through the septal defect. These currents are generated in the swirls of blood entering through the venae cavae.

Dilatation of the right atrium, right ventricle, and pulmonary trunk and hypertrophy of the right ventricle occur in response to the large quantity of blood delivered through the shunt. In later periods, when there is increased pulmonary resistance and elevation of the pressure in the right atrium, the shunt may be gradually reduced, until it may become very little, or lead to brief or prolonged periods in which the shunt is into the left atrium.

Pathologic Classification of Interatrial Septal Defects

The types of defects occurring in the interatrial septal complex include those frequently observed to those of rarity. These are discussed in detail in textbooks and in atlases by several authors including Abbott,[2] Edwards,[3] Edwards *et al.*,[4] Lev,[5] Moragues and Lynxwiler,[6] Kjellberg *et al.*,[7] and others.

I. Defects involving region of foramen ovale

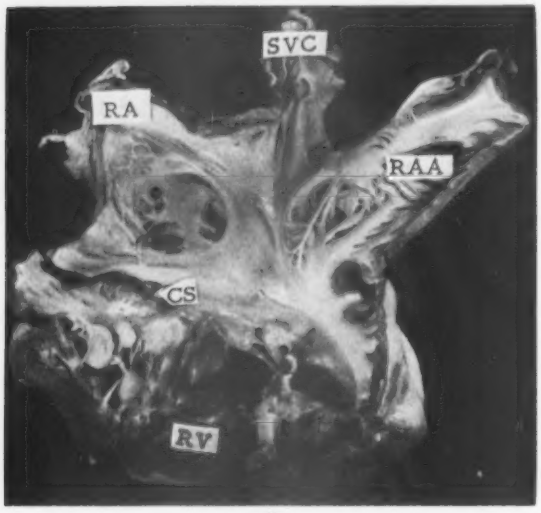
(*A*) *Probe Patent Foramen Ovale:* This is observed in 12 to 25 per cent of otherwise normal adult human hearts. In these cases a probe can be diagonally passed upward from the right atrium into the left through the foramen ovale beside the flap of the foramen ovale. This condition, considered a normal finding, usually lacks significance because the higher pressure in the left atrium forces the flap of the septum primum against the foramen ovale, and prevents any shunt of blood.

(*B*) *True Patency of Foramen Ovale Complex:* Actual defects of the region of the foramen ovale including the foramen secundum may give rise to shunts (Fig. 1–3). The mechanism producing these are: (1) an inadequate flap of the septum primum which fails to bridge the foramen ovale (Fig. 3); (2) defective development of the septum secundum giving rise to a large foramen ovale; (3) the formation of fenestra in either the valve of the septum I or in abnormal sites in either the cephalad or caudal part of the septum primum (Fig. 2).

The larger defects are produced by combinations of these but isolated forms are not uncommon in the smaller openings. The defects can differ considerably in size and shape. Those which are less than 0.5 mm in diameter are considered to be physiologically innocent. Others of large size may considerably embarrass the heart because of the great handicap imposed by large shunts of blood into the pulmonary circulation.

II. Defects involving the caudal portion of the interatrial septum

A communication between the atria in the caudal portion of the septum is much less frequently observed than those of the foramen ovale complex. The latter is usually formed and obliterated in these cases. There are two prevailing concepts concerning the mechanism of development of these defects. One opinion considers that the essential problem arises from failure of the advancing edge of the septum primum to become fused to the endocardial cushions. Another idea is that the primary defect is failure of complete formation of the endocardial cushions and the lack of provision for a complete connection with the septum primum. Either changes in the interventricular valves or a common atrioventricular canal are situations beyond the scope of our discussion. Some authors such as Wakai and Edwards[8] and Campbell and Missen[20] consider this entity as being a milder form of either persistent common atrioventricular canal or of endocardial cushion defect. We agree with Lev[10] that inclusion of this defect, with the interatrial grouping, is justified because of their similar clinical course and outlook. Defects of the foramen primum type may be coupled with abnormal entry of either the inferior



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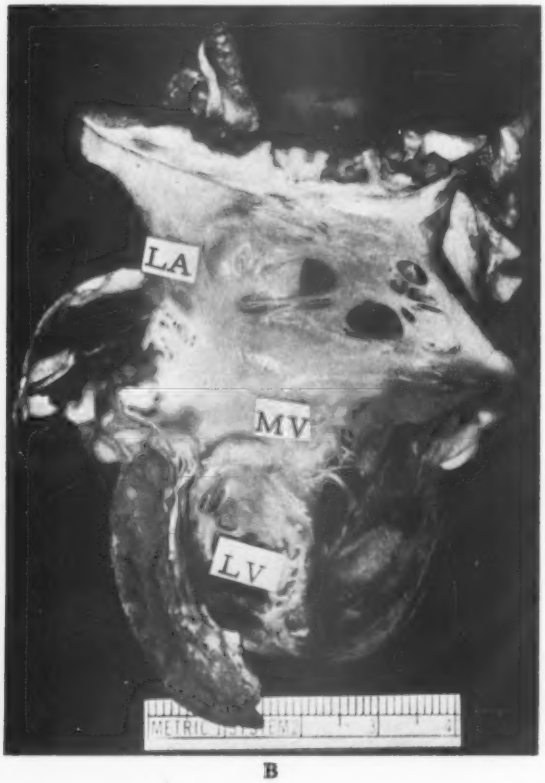

B

Fig. 2. Large patent foramen ovale—fenestrated type. (A) view from right atrium showing large foramen ovale bridged by fenestrated valve of septum secundum. RA—right atrium; SVC—superior vena cava; RAA—right auricular appendage; CS—coronary sinus; RV—right ventricle. (B) View from left atrium; shows large areas of resorption of interatrial septum I, many overlying the foramen ovale; others overlying the interatrial septum II. LA—left atrium; MV—mitral valve; LV—left ventricle.

vena cava, coronary sinus or pulmonary veins. One may postulate that abnormal blood currents from these veins disturb the usual obliterating process of the foramen primum.

III. ATRIAL SEPTAL DEFECTS IN CEPHALAD LOCATIONS

This grouping includes the high, unusually located defects. These defects involve the cephalad part of the atrial septum and are uncommonly observed. Lewis and Taufic[11] describe this type defect as usually being located beneath the superior vena cava, separate from and above the fossa ovalis, and lacking a complete margin, because the cephalad atrial wall usually forms a part of its boundary. They stress the common association of this defect with an anomalous pulmonary vein or veins. They conclude that this may represent an abnormal entry of the superior vena cava into both right and left atria, rather than a failure of a part of the septum to develop in this cephalad position.

IV. DEFICIENCY OF ENTIRE ATRIAL SEPTUM

In instances of a single atrium either a vestigial ridge or less commonly a smooth surface without attempt at subdivision may be observed. Both auricular appendages are usually developed. The vessels often enter in their usual positions. These cases occur in both cor biloculare and cor triloculare biventriculare. In the former type, a hopeless outlook is usual. In some cases of cor triloculare biventriculare, the development of a plastic septum may be accomplished.

Individually, cases may be uncommonly complex because of the presence of more than one type of interatrial communication. These may be recognized preoperatively, but are more likely to be uncovered during inspection of the atrial septum.

Commentary on Associated Pathological Changes

There are numerous associated pathological features which are seen in cases of atrial septal defects. Many of these are sequelae of the shunt of blood through the defects, while others represent complications, developing in the

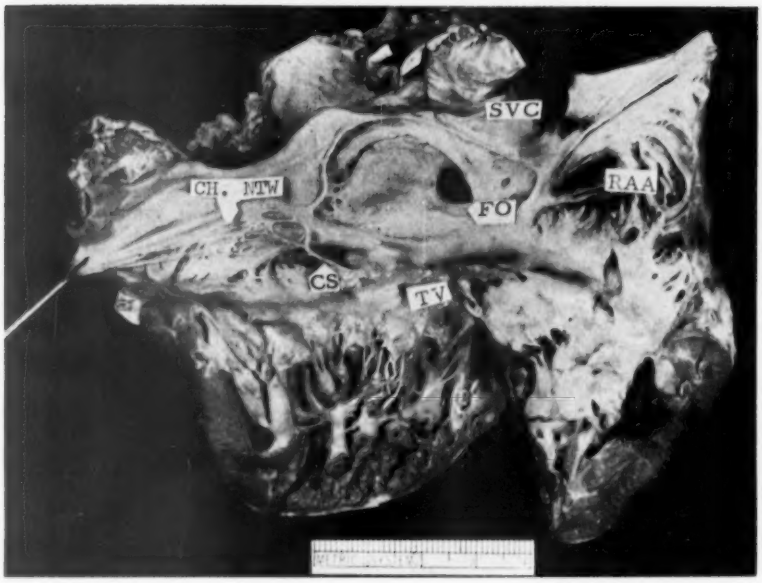

Fig. 3. Interatrial septal defect showing a short valve of septum primum failing to completely bridge foramen ovale. CH.NTW—Chiari network; CS—coronary sinus; FO—foramen ovale; SVC—superior vena cava; TV—tricuspid valve; RAA—right auricular appendage.

natural course of the anomalies. These various entities are separately discussed.

Incidence of Combined vs. Isolated Lesions: Interatrial septal defects associated with other anomalies are considerably more common than ones of pure type. Abbott[2] in a series of 1,000 cases of congenital cardiac disease found 400 instances in which an interatrial septal defect was observed. Of these only 73 were classified as being of pure type. These include 40 cases involving the foramen ovale complex; 10 appearing in the superior part of the atrial septum; 18 occurring in the caudal part of the septum and 5 in which multiple parts of the septum had defects. In 327 cases the defect was a part of combined anomalies of wide variety. In one of three cases of premature closure of the foramen ovale another type of interatrial septal defect and a patent ductus arteriosus was found. Other investigators[3,4,5,7,14] have had similar experiences.

Atrial septal defects are always seen in tricuspid atresia, entry of the pulmonary veins into the right atrium and almost always in complexes in which there is hypoplasia of the aorta. These defects are often associated with either transposition complexes, pulmonary stenosis or in any form of congenital heart disease. Therefore, any surgical corrective procedure should include an evaluation for presence of such a defect.

Size of Defects: Physiologically, defects less than 0.5 cm in diameter have been said to be clinically insignificant. Defects of greater size manifest shunts which may give rise to symptoms. When defects are greater than 2.0 cm in diameter, they are usually accompanied by definite symptoms. Generally, the larger the defect, the greater the degree of shunt and cardiac embarrassment. In Lutembacher's syndrome the interatrial septal defects are described as being large, usually in the order of 3.0 to 6.0 cm in diameter. However, Erickson and Willius[19] report a case in a 68-year-old white male who had a defect of the foramen ovale complex measuring 10 × 7 cm, wherein a normal sized heart could be snugly fitted.

Abnormal Drainage of Pulmonary Veins: The pulmonary veins, usually the right, may abnormally drain into either the right atrium, coronary sinus, or superior vena cava (Fig. 4). Various authors find the incidence of this to range between 10 and 20 per cent of cases. Less common terminations, according to Lewis

Fig. 4A. Abnormal drainage of pulmonary veins of middle and lower lobes of right lung and of left lung into coronary sinus—interatrial septal defect. View showing right atrial wall reflected to the left to expose course of pulmonary veins into coronary sinus.

Fig. 4B. Abnormal drainage of pulmonary veins of middle and lower lobes of right lung and of left lung into coronary sinus—interatrial septal defect. View showing retraction of right atrial wall to right to expose interior of right atrium. RPV—right pulmonary vein; LPV—left pulmonary vein; CS—coronary sinus; IASD—interatrial septal defect; RA—right atrium; TV—tricuspid valve; RV—right ventricle.

and Taufic,[11] in descending order of frequency are the left innominate vein, azygous vein, portal vein, ductus venosus, and inferior vena cava. The surgeon should be aware that when he observes highly oxygenated blood entering the right atrium that it may be coming from sites other than an interatrial septal defect. Clinical recognition of these combinations of anomalies will enhance the necessary surgical revision.

Size of the Heart and Major Vessels: Cases with defects of physiologic significance usually have dilatation of the right atrium, right ventricle and pulmonary artery (Fig. 5). The left ventricle is either normal in size or somewhat smaller than expected. Hypertrophy of the right ventricle of varying degrees is dependent upon the volume of blood flow and pulmonary resistance. The aorta is either normal in size or somewhat smaller than usual. Some hearts, probably due to lesser degrees of shunt, fail to have any significant enlargement. In some cases atherosclerotic changes have led to the development of aneurysms of the pulmonary artery or its main branches.[3]

Fig. 5. View of posterior aspect of heart to show relatively great dilatation of pulmonary artery and hypoplasia of aorta.

Changes in the Intrinsic Pulmonary Vasculature: In cases in which pulmonary hypertension has developed, the small intrinsic muscular pulmonary arteries, less than 1,000 micra in diameter, may exhibit varying degrees of widening of the walls and narrowing of the lumens (Fig. 6).

Fig. 6. Case 2. Large intrinsic pulmonary arteries of right lung showing intimal atherosclerosis.

Studies with Verhoeff's elastic stain and van Gieson counterstain permit demonstration of the nature of the thickening, fraying and reduplication of the elastic lamellae, the proliferative intimal thickening, endothelial change, medial hypertrophy and the adventitial fibrosis (Fig. 7). The arterioles often show thickened prominent elastic lamellae. These lesions have been demonstrated by many investigators as the response to sustained high intrapulmonary vascular pressure. Frozen sections of a portion of lung taken at the time of operation often render an appraisal of its degree, so that the surgeon has an opportunity to alter his method of handling the case, with the use of such information.

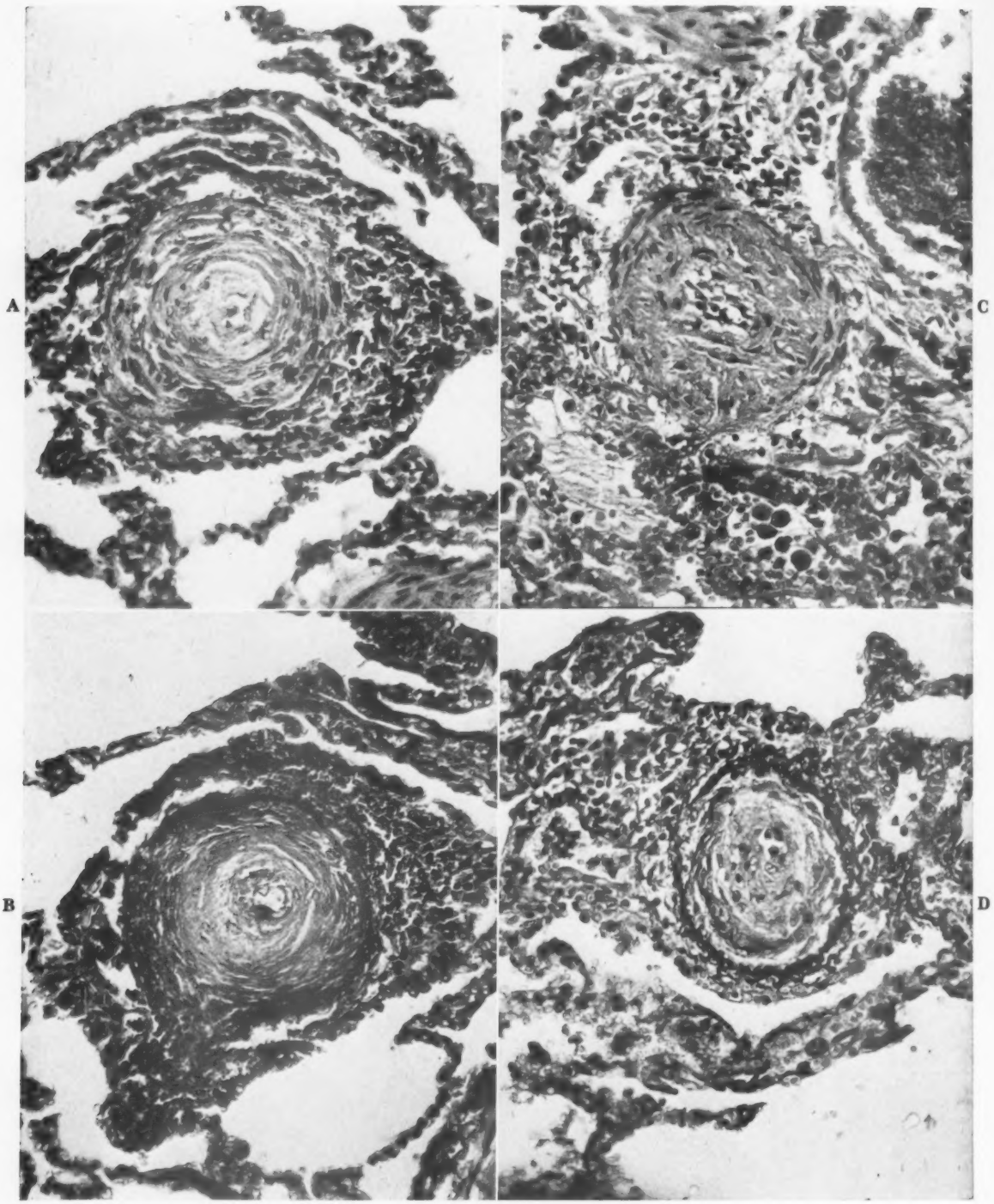

Fig. 7. Case 1. Female, aged 40 years (A and B). Case 2. Female, aged 36 years (C and D). Marked small arterial disease in response to sustained high pulmonary arterial pressure. (A) and (C) Hematoxylin-eosin stain × 250. Marked intimal cellular proliferation, hyaline deposits, tiny lumen. (B) and (D) Verhoeff's elastic—Van Gieson stain × 250. Marked intimal thickening, irregular elastica in perimeter of vessel, lack of good definition of various histologic layers in B, thick dense elastica in D.

Heath and Whitaker,[12] in a study of the small pulmonary blood vessels in atrial septal defect, found that three of the five women studied had increased pulmonary arterial mean pressures of 58, 70, and 108 mm Hg, and each showed definite medial hypertrophy, severe intimal proliferation, and thick adventitia in vessels between 100–1,000 micra and a distinct muscular media with two elastic lamellae in arterioles less than 100 micra in external diameter. In two women with pulmonary arterial mean pressures of 16 and 20 mg Hg no such changes could be demonstrated. It is of interest to recognize that most cases, despite great increments of pulmonary blood flow, may have normal mean pulmonary arterial pressures, hence no changes in the small pulmonary vasculature. Diagnosis and correction of the defects in these cases in the period prior to development of pulmonary hypertension is an important factor in the ultimate prognosis.

Welch and Kinney[13] in a study of 25 cases of atrial septal defect found that 13 were uncomplicated by additional cardiac anomalies and that the pulmonary vascular lesions were of no greater significance than in the control group of comparable ages. One of these cases had a pulmonary arterial pressure of 35/10 mm Hg and a pulmonary flow of 14 *l*/min.

Paradoxical Thromboembolism: In cases of atrial septal defect the development of massive thromboembolism leads to acute cor pulmonale. This high pressure in the right atrium will cause a reversal of the shunt which would cause all further emboli to be carried through the opening into the systemic circulation. Edwards[4] cites an interesting case in which a large thromboembolus became impacted in an atrial septal defect.

Defect Between the Left Ventricle and Right Atrium: A rare defect is the presence of a communication through the membranous part of the interventricular septum which separates the right atrium from the left ventricular outflow tract. This anomaly is easily recognized on the basis of the jet of oxygenated blood entering the right atrium.

Lutembacher's Syndrome: A special entity, known as Lutembacher's syndrome,[18] is characterized by a sizeable congenital interatrial septal defect with mitral stenosis (Fig. 8). The latter is usually of rheumatic origin but may rarely be congenital. The rheumatic form of mitral stenosis may, therefore, be considered as a complication of interatrial septal defect. This condition has a greater than 2 : 1 predominance in females. In our experience the syndrome is uncommon. Cases with a large interatrial septal defect and the presence of rheumatic changes in the mitral valve without stenosis, should not be classified as Lutembacher's syndrome. In cases with rheumatic mitral stenosis and small interatrial septal defect there is likewise no justification for inclusion in this category. The interatrial septal defect is usually a large patent foramen ovale, but defects of the caudal type of the interatrial septum have been described. The development of mitral stenosis in these cases elevates the left atrial pressure, which in turn results in a greater degree of shunt through the interatrial septal defect. The greater the shunt, the more progressive becomes the dilatation and hypertrophy of the right cardiac chambers and of the pulmonary arteries. Development of high pulmonary arterial pressures leads

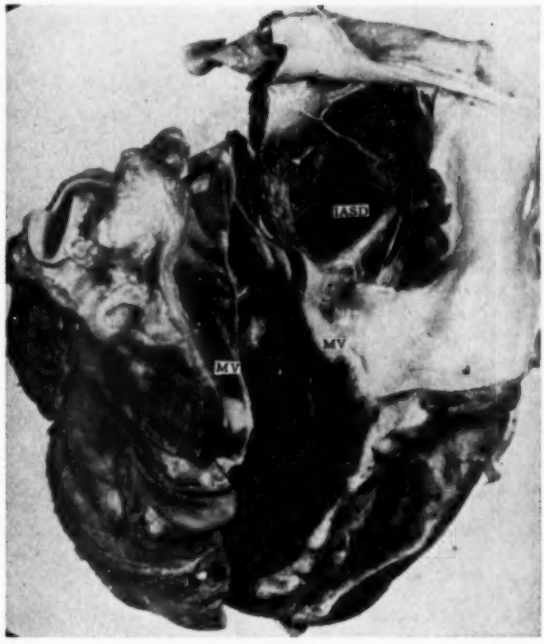

Fig. 8. Lutembacher's syndrome—large interatrial septal defect; stenotic mitral valve (shows rheumatic stigmata—landmarks distorted due to sectioning); IASD—interatrial septal defect; MV—mitral valve.

to changes in the small muscular pulmonary arteries and arterioles as previously described.

A syndrome, like that of Lutembacher's, may arise in cases developing either mitral insufficiency, aortic stenosis or systemic hypertension. Bailey[1] stresses that, during surgical repair of the mitral valve, the atrial septum should be examined for presence of a defect. He is also of the opinion that in correcting atrial septal defects the character of the mitral valve should be ascertained as well.

Miscellaneous Atrial Septal Conditions: Among these are premature closure of the foramen ovale, aneurysm of the fossa ovalis, and with extreme rarity an acquired perforation of the interatrial septum in subacute bacterial endocarditis.

Clinical and Prognostic Features

Isolated patency of the interatrial septum may be present for many years without symptoms. Occasional cases have been discovered in old people who had led active lives without suspicion of a cardiac anomaly. Many cases are recognized by discovering a murmur during routine physical examination. It should be emphasized that many patients do not develop symptoms until later in life.

Clinical Features: The usually described clinical manifestations are: a higher frequency in females, frail build, retarded growth in children, underweight, absence of cyanosis, shortness of breath, diminished tolerance of physical activity, frequent respiratory infections and occasional distortion of the precordial region of the left side of the thorax. The frequently described physical findings include a systolic murmur heard loudest in the second or third intercostal space along the left sternal border (not always present), a loud and split second pulmonic sound with accentuation of the second part, commonly a soft apical diastolic murmur, and usually cardiac enlargement.

Radiologic changes of the chest show enlargement of the right atrium, right ventricle and pulmonary artery. Accentuated hilar pulsations, prominent vascularity of the lung fields and occasionally aneurysmal dilatation of the pulmonary artery are also observed. Angiocardiography may help greatly in defining the position of the defect as well as uncovering other anomalies.

Physiologic studies by cardiac catheterization have contributed vastly to accurate diagnosis through differences in oxygen saturations, pressures in cardiac chambers, or by chance passage of the catheter through a defect into the left side of the heart. Electrocardiograms often show right axis deviation, incomplete to complete bundle branch block and infrequently atrial fibrillation. In arachnodactyly the presence of a heart murmur usually is caused by an atrial septal defect. In mongolism such a defect[14] is usually a persistent common atrioventricular canal.

Prognostic Features: The natural prognosis, despite the reports of people living into advanced age, is poor in the light of normal life expectancy. The average age of death, in groups of cases, by different authors are: Roesler[15] (1934) 36 years; Burrett and White[16] (1945) 37 years; and Campbell *et al.*[9] (1957) 30 years. The presence of cardiac failure is considered to be a poor prognostic sign. Metianu and Durand (1954), quoted by Campbell *et al.*,[9] found that the onset of atrial fibrillation usually was consistent with death occurring within a year. Some of these patients die unexpectedly without explanation for its immediacy. Usually death occurs with either congestive cardiac failure, pulmonary thromboembolism, pulmonary infarcts, or bronchopneumonia. Deaths have occurred from superimposed subacute bacterial endocarditis, brain abscess, paradoxical cerebral thromboembolism and epileptiform convulsions. Campbell *et al.* in discussing the natural prognosis in the study of 100 cases found that the first two decades of life had a good outlook except for some physical limitation. In 95 per cent the patients were doing well at 20 years and 85 per cent at 30 years. The period of deterioration progressively became greater after the age of 40 years. Statistically they found this to be especially of importance in males because in their cases, an incidence of 30 girls and 22 boys could be found in the age under 20 years; whereas they had 42 females and 6 males at the age of 40 years. The death rate in open cardiac surgery has rapidly dropped since the established use

TABLE I

Significant Data Observed at Autopsy in Seven Cases of Interatrial Septal Defect

Case	Age and sex	Type of defect	Size of defect (cm)	Heart changes	Cardiac catheterization pressures (mm Hg)			Pulmonary vasculature	Cause of death
					RA	RV	PA		
1 (RS)	40 F	Foramen ovale complex	3.7 × 2.5	Marked right ventricular hypertrophy, especially of conus. Dilated right atrium	7/3	80/4	80/48	Marked dilatation of pulmonary artery. Marked atherosclerosis. Marked sclerosis of small pulmonary vessels	Died first postoperative day with recent thrombosis of right pulmonary artery. Closed heart operation
2 (AML)	36 F	Foramen ovale complex	1.8 × 1.1	Heart weight 500 g. Marked right ventricular hypertrophy. Moderate hypoplasia of aorta	4/1/2	125/20	—	Marked dilatation of pulmonary artery. Marked atherosclerosis. Moderate to severe sclerosis of small pulmonary vessels	Died 7th postoperative day. Recent thrombosis of right pulmonary artery. Exploratory closed operation for suspected tetralogy
3 (SM)	28 F	Foramen ovale complex	3.2 × 2.8	Heart weight 340 g. Moderate hypertrophy of right ventricle. Dilated right atrium. Hypoplasia of left ventricle and aorta	9/3	68/6	70/30	Marked dilatation of pulmonary artery. Marked atherosclerosis. Moderate to marked sclerosis of small pulmonary vessels	Died 1st postoperative day. Marked pulmonary edema, hyperemia and widespread hemorrhage. Closed heart operation
4 (GJ)	5 M	Caudal defect. Normal foramen ovale closed	1.5 × 1.0	Heart weight 100 g. Marked right ventricular hypertrophy (normal heart weight—73 g)	11/6	40/3	27/12	Moderate dilatation of pulmonary artery. No pulmonary vessel changes	Died 7 hr postoperatively. Marked pulmonary edema, hyperemia, and hemorrhage. Open heart operation
5 (JK)	59 M	Foramen ovale complex	1.2 × 0.5	Heart weight 420 g. Left ventricular hypertrophy. No changes in right ventricle	—	—	—	No dilatation of pulmonary artery. No pulmonary vessel changes	No operation. Died 2nd hospital day. Lobar pneumonia (RUL). Multiple thrombi in pulmonary artery and left midcerebral artery. Paradoxical thromboembolism
6 (DF)	8 (mo) F	Foramen ovale complex	2.0 × 2.0	Heart weight 42 g. Right ventricular hypertrophy (normal heart weight 37 g)	—	—	—	Moderate dilatation of pulmonary artery. No pulmonary vessel changes	No operation. Died 2nd hospital day. Marked dehydration, undernourished. Acute gastroenteritis
7 (HK)	39 F	Foramen ovale complex. Lutembacher's syndrome	6.5 × 7.0	Heart weight 550 g. Dilated right atrium and right ventricle. Mitral stenosis. Hypoplasia of aorta	14/5	48/0	40/18	Dilated pulmonary artery. Insignificant changes in small pulmonary arteries and arterioles	Closed heart operation. Died 5th postoperative day, after attack of high fever and severe dyspnea

of the heart-lung bypass and direct visual repair.

Presentation of Our Autopsy Cases

Incidence of Various Types of Defects

Patent Foramen Ovale: In a review of our general autopsy material we found 24 per cent to have the presence of a probe patent, valve competent, foramen ovale. In an additional six cases, five of whom were female, we encountered small openings in the region of the foramen ovale. These defects ranged from 0.2 to 0.4 cm in diameter and occurred as either a crescentic gap between the valve of the septum primum and the edge of the foramen

ovale, or as a single or small group of perforations of the septum primum. These patients ranged from 58 to 80 years of age and died as a result of either cancer, pyelonephritis or bronchopneumonia. No murmurs were recorded in any of these cases. There were no pathologic changes in either the right side of the heart or the pulmonary artery. These findings support Luisada's[17] conclusion that the shunt in interatrial septal defects of less than 0.5 cm in diameter is too small to be of physiologic significance.

Atrial Septal Defects with Associated Anomalies: In 86 autopsies upon subjects with congenital anomalies of the heart, we have found 48 cases (55 per cent) to have interatrial septal defects. In 41 of the cases we found one or more additional associated anomalies which included interventricular septal defects, patent ductus arteriosus, transposition of great arterial trunks, pulmonic and subpulmonic stenosis, persistent common atrioventricular canal, coarctation of the aorta, atresia of the tricuspid valve and others as listed in Table II. In some instances the defects were small, in the order of 0.3 to 0.5 cm in diameter, but are included in the evaluation since they appeared in the infants and small children. The significance of the shunt in this age group is difficult to determine in the light of the other anomalies. These figures agree with the experience of others in finding interatrial defects to be of frequent occurrence in conjunction with other anomalies.

TABLE II

Associated Anomalies Encountered in 41 Cases with Interatrial Septal Defects

Interventricular septal defects	19
Patent ductus arteriosus	14
Transposition of the great arterial trunks	8
Coarctation of aorta	6
Dextroposition of aorta	5
Pulmonic stenosis	5
Persistent common atrioventricular canal	3
Infundibular stenosis	3
Atresia of tricuspid valve	3
Hypoplasia of pulmonary valve and artery	3
Cor triloculare biatriatum	3
Absence of ductus arteriosus	2
Single coronary artery	2
Superior and inferior venae cavae emptying into left atrium	2
Anomalous pulmonary veins emptying into right atrium	1
Absence of mitral valve	1
Absence of main pulmonary artery	1
Persistent conus	1
Tricuspid stenosis	1
Anomalous coronary sinus draining pulmonary venous trunks	1

In the remaining seven cases of pure interatrial septal defects, one was complicated by mitral stenosis of rheumatic origin which we have classified as Lutembacher's syndrome. Table I reveals the essential pathological features found in these cases.

Isolated Atrial Septal Defects: The six cases of isolated atrial septal defects, exclusive of the case of Lutembacher's syndrome, include five occurring in the region of the foramen ovale complex and one appearing in the caudal part of the septum. Four of these cases were observed in females. Cases 1, 2, and 3 were women in the third to fifth decade who had the usual symptoms, which had become more severe in the recent years prior to study and were complicated by severe pulmonary hypertension. Physical examination and clinical studies all included typical findings. In case 2, moderate cyanosis had been present for several months. Operations in these patients were performed during the period in which a closed technic utilizing the atrial wall to bridge the defect was necessary. Patients 1 and 2 died on the first and seventh postoperative days, respectively. Each had recent and organizing thrombosis of a main stem and branches of the pulmonary artery as the major finding. The third patient, who had had a previous attempted closure six months before, succumbed with severe pulmonary edema on the first postoperative day. Case 2 illustrates the reversal of shunt occurring with a great increase in pulmonary pressure.

All three cases, especially the two in which the pulmonary artery thrombosis occurred, had severe dilatation of the pulmonary vasculature, marked intimal atherosclerosis and moderate to marked changes in the small muscular pulmonary arteries and arterioles. In the smaller vessels the changes included intimal proliferation and thickening, endothelial prominence,

splitting, reduplication and fraying of the elastica, medial hypertrophy with occasional hyalinization and adventitial fibrosis. These findings correlate well with the increased pressure present in the right ventricle and pulmonary arteries as measured by cardiac catheterization.

Case 4, the only death occurring in the group in which the heart-lung bypass and open technic were utilized, was that of a four-year-old child with a large caudally located interatrial septal defect. This defect was considered to be consistent with partial retention of a foramen primum. There were no conduction changes either during or after the operation as observed in the electrocardiographic monitor. The principal autopsy findings, other than the changes in the heart, were severe pulmonary edema, hyperemia and recent hemorrhage.

Cases 5 and 6 were found at autopsy, without previous cardiac studies and definitive diagnosis. In case 5, the defect was moderate in size (1.2 × 0.5 cm), involving the region of the foramen ovale complex, and apparently existing without clinical changes developing. He was 59 years of age, a chronic alcoholic, and brought to the hospital after suddenly becoming unconscious. Clinically he had consolidation of the upper lobe of the right lung and a right hemiplegia. He died after two days without regaining consciousness. Autopsy revealed lobar pneumonia in the stage of gray hepatization. He had no significant changes which could be considered to be stigmata of an increased shunt flow to the right side of the heart or to the pulmonary artery. However, there were multiple thrombi in many portions of the pulmonary vascular tree which were similar in nature to a thrombus occluding the left middle cerebral artery. On the basis of the nature of the thrombi in the two sites, the presence of the interatrial septal defect, and the abruptness of the onset of unconsciousness we considered that this case represents one of paradoxical thromboembolism. It is of importance to recognize that a defect which may not be physiologically significant may serve as a passageway for this serious complication.

In case 6, an eight-month-old girl, death clinically resulted from the effects of severe diarrhea, dehydration and malnutrition. She had a systolic precordial murmur, cardiac enlargement and a prominent pulmonary conus as observed by x-ray. Although a clinical diagnosis of congenital heart disease was made, no definitive studies could be carried out. The large interatrial septal defect (2 × 2 cm) certainly was a significant factor in her inability to recover from the effects of the gastroenteritis.

Lutembacher's Syndrome: The case of Lutembacher's syndrome occurred in a 39-year-old white housewife, who had had a series of admissions because of increasing dyspnea. This began during childhood while playing, but throughout the years had progressed until it was almost continuous. She had a history of frequent sore throats and respiratory infections. Clinically, she presented a precordial systolic murmur, a diastolic murmur in the tricuspid area, and a thrill over the apical region. A diagnosis of chronic rheumatic heart disease with mitral stenosis had been made prior to cardiac evaluation. A chest x-ray showed enlargement of the ventricles and of the pulmonary conus. An electrocardiogram revealed right bundle branch block and atrial fibrillation.

Cardiac catheterization revealed the catheter to pass through an interatrial septal defect. The pressures were: right atrium—14/5, right ventricle—48/0 and pulmonary artery—40/18. An operation on July 17, 1952 for repair of the interatrial septal defect and splitting of the mitral valve was carried out. Her immediate postoperative period was uneventful, but on the 5th postoperative day she developed severe dyspnea, violent cough and high fever. She died shortly afterward.

Autopsy revealed the heart to weigh 550 g. There was considerable dilatation of the atria, right ventricle and pulmonary arteries. There was no significant thickening of the walls of the small pulmonary arteries and arterioles. The left ventricle and aorta were relatively small. There was a large fenestrated interatrial septal defect involving the foramen ovale complex measuring 6.5 × 7.0 cm. The mitral valve, showing two commissurotomy wounds, was described as being typically of "fish-mouth" character and measuring 2.5 × 1.0

cm in cross diameters. The leaflets were thickened, the commissures largely obliterated, and the chordae tendineae shortened, thickened and fused. Definite rheumatic stigmata were present in the aortic and tricuspid valves. This case illustrates that a large shunt flow resulting from a giant interatrial septal defect and a mitral stenosis does not necessarily indicate that sclerotic changes in the small pulmonary vasculature are present.

Unusual Cases Exhibiting Abnormal Venous Drainage

The following two cases are included in order to emphasize the problem of abnormal drainage of pulmonary veins and venae cavae. These cases illustrate situations with which a surgeon may be faced when there is both shunting of blood through an atrial septal defect and the presence of abnormal venous entries.

Pulmonary Venous Drainage into Coronary Sinus: In one case, a four-year-old white female, a typical history, physical findings and clinical studies indicative of interatrial septal defect were found. The cardiac catheterization pressures were: right atrium—8/4, right ventricle—40/3 and pulmonary artery—42/22.

During operation, employing the heart-lung bypass, the heart was discovered to have a relatively great size of the right atrium with a posterior and lateral prominent bulging. In the floor of this bulge was a large opening through which oxygenated blood flowed in large quantities. This was considered to be the interatrial septal defect and attempts to close this were begun. A further evaluation revealed that actually this was the coronary sinus with pulmonary veins from both lungs entering into it. A surgical rearrangement of this vascular anomaly was carried out and the interatrial septal defect in the region of the foramen ovale complex was demonstrated and closed. Postoperatively she developed cyanosis, marked restlessness and severe dyspnea. She died after $11^1/_2$ hours.

Autopsy revealed the pericardial sac to be securely closed with a continuous suture and to be distended with 75 g of liquid and clotted blood. The heart weighed 130 g (normal weight 73 g). The interatrial septal defect measured 1.0 × 0.6 cm. This appeared in the region of the foramen ovale with a short valve of interatrial primum I failing to guard the passageway. Examination of the pulmonary veins revealed those from the left lung and the middle and lower lobes of the right lung joining to form a common trunk which drained into the coronary sinus. A vein from the upper lobe of the right lung entered into the left atrium.

Anomalous Drainage of Pulmonary Veins and Inferior Cava: The second case, a white female, aged 32 years, underwent cardiac evaluation because of progression of dyspnea with exertion, easy fatigability, and frequent epistaxis beginning during childhood. On evaluation, her findings were interpreted as interatrial septal defect and abnormal drainage of pulmonary veins into the right atrium. The catheterization pressures were: right atrium—9/5, right ventricle—38/2 and pulmonary artery—20/7.

During the operation employing the heart-lung bypass, the right pulmonary veins were shifted to the left atrium. There was a large caudal type of defect. The inferior vena cava emptied into the floor of the defect. The free margin of the defect was sutured to the atrial wall, on the apparent medial side of the inferior vena caval opening. Postoperatively, her condition was not remarkable except for a slight degree of cyanosis. She was discharged as improved after two weeks. One month later she was readmitted in severe shock with cyanosis and complaining of dull pain situated deeply in the midportion of her back. Her condition rapidly deteriorated and she died on the second hospital day.

Autopsy revealed the heart to have a foramen primum type of interatrial septal defect measuring 3.0 × 2.5 cm. The caudal wall was formed by tissue overlying the atrioventricular valves and interventricular septum. The posterior wall revealed a smooth atrial lining. The inferior vena cava entered the left atrium in such fashion that its right edge was in line with a plane meeting with the free margin of the septal border of the defect. In the closure, the lumen of the inferior vena cava had been constricted to half of its diameter, but drained into the right atrium as a result of the direction

of the suture line. A narrow residual circuitous passageway opened from the inferior vena cava into the left atrium through the sutured site. A large thrombus, largely filling the hepatic vein and intrahepatic veins, projected into the inferior vena cava. There were multiple true and Zahn's type infarcts of the liver and multiple recent infarcts of both lungs and both kidneys. There were central necrosis and marked chronic passive hyperemia of the liver with a hemorrhagic ascites.

In the light of the rapid progression of the symptoms, this case was considered to have developed a Chiari's type syndrome. In retrospect, the approximation of the edges of the inferior vena cava by a tape tourniquet led to apposition of the edges of the atrial wall in the floor of the defect. The folds which were produced, in part, simulated a ridge interpreted as the atrial mural boundary of the defect. The suture line had been established along this plane. Thus the placement of occluding tapes about either of the venae cavae when dealing with either cephalic or caudal defects may give rise to problems due to artificial folds. It should be emphasized that setting the tourniquets as far away from the atrium as possible will avoid such artefacts.

Commentary on Our Clinical Material

In this pathologic study the meagerness of autopsy material of pure interatrial septal defects reflects the relatively benign outlook in surgical correction of these anomalies. Excluding these autopsies, 81 cases of uncomplicated atrial septal defects have been studied in our cardiopulmonary laboratory. In order to provide a more informative survey, we are including data observed in the 23 patients who underwent open heart surgery. These 23 patients ranged from 5 to 39 years of age. All were Caucasians. There were 13 females and 10 males. All but two of these cases were symptomatic. The remaining two were recognized during physical examination for respiratory infections. The majority of these patients exhibited the usual clinical findings. In three cases, aged 39, 15, and 6 years, slight elevation of pulmonary arterial pressures were found. In the other cases, the pressures were normal.

During operation the defect in 19 cases involved the foramen ovale complex. They ranged from being circular to irregular in shape and from 1.5 × 2.0 cm to 4.5 × 5.0 cm in cross diameters. In two cases, the defect was of caudal type, and considered to be a partially retained foramen primum. These measured 2.5 and 3.0 cm in diameter. The caudal margin of these defects was formed in part by tissue overlying the interventricular septum and by posterior atrial wall. The two remaining cases were classified as occurring in the cephalic part of the interatrial septum. One measured 2.0 cm in diameter and the other was described as a small defect.

In the remaining 58 cases, 16 patients have undergone a closed type of repair and the remainder have not been operated upon at this time. In the period prior to open cardiac surgery, three cases of Lutembacher's syndrome have been accepted because of surgically demonstrated large interatrial septal defects and true mitral stenosis of rheumatic origin. All of these cases underwent a closed type of atrial septal repair and a mitral commissurotomy. These patients were females aged 29, 30, and 32 years.

Summary

In this presentation, the highlights of interatrial septal defects are reviewed from the embryologic, anatomic, pathologic, and clinical aspects. Sxi cases of atrial septal defect and one of Lutembacher's syndrome are discussed, with the salient clinical and autopsy findings. In three cases having high pulmonary arterial pressures, the changes in the pulmonary vasculature are stressed. In two cases of abnormal venous drainage, the problems confronting the surgeon are discussed. The paucity of autopsy material in our series directly reflects the low mortality rate which has been achieved with definitive surgery utilizing the heart-lung bypass.

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Pathologic Physiology of Lutembacher Syndrome*

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IT WAS the first comprehensive description by the French physician Lutembacher[1] in 1916 that raised this entity to the dignity of a syndrome, although according to McGinn and White[2] the case reports of interatrial septal defects associated with mitral stenosis had periodically appeared in earlier literature at least 15 times since the first description by Martineau in 1865. Etiology of this condition has been variously postulated all these years.

ETIOLOGY

Firket[3] in 1880 considered the mitral lesion to be congenital in origin and the interatrial septal defect to be an additional malformation. Lutembacher[1] proposed that the congenital mitral stenosis could be responsible for the patency of the septal defect by preventing the closure of the foramen ovale through maintenance of a left-to-right shunt by virtue of having a higher pressure in the left atrium. This line of reasoning did not hold ground for reasons obvious today. A higher pressure in the left atrium would rather tend to favor the closure and not the patency of the foramen ovale. Excessively dilated atria may conceivably contribute toward patency of this foramen by stretching the valves, yet such an opening hardly, if ever, attains any clinical significance. Dressler and Roesler[4] pointed out that if mitral stenosis were to be responsible in some way for the maintenance or production of atrial septal defect, these two should be expected to occur together with greater frequency than is commonly found. Griesser[5] stresses that with the availability of the successful surgical relief for the acquired mitral stenosis it becomes important to distinguish it from the one of congenital origin for which nothing can be done surgically.

The congenital nature of the mitral stenosis has been seriously questioned in this condition. According to Ferencz *et al.*[6] no case report exists in the literature of mitral stenosis that is undeniably congenital and associated with a significant defect in the interatrial septum. The authors reported nine cases of their own and sorted 34 cases from the survey of literature since 1846, and none of these were associated with an interatrial septal defect, although other malformations, principally of the aortic valve, accompanied a great number of them. Hyperplasia of the right ventricle coupled with hypoplasia of the left side was at one time regarded as the congenital basis in this syndrome, but the dynamic theory has completely replaced that concept. It is now generally accepted that in these cases of Lutembacher syndrome, a congenital atrial septal defect of one kind or another exists and the mitral lesion is acquired later, on a rheumatic basis. Taussig[7] believes that the presence of the septal defect acts as a precipitating cause for rheumatic involvement.

INCIDENCE AND DEFINITION

The advent of open heart surgery has further revised the impression about the true incidence of this syndrome. Most authors now agree that it occurs rather infrequently as compared to previous reports in the literature.[8–10] At St. Vincent Charity Hospital six cases of Lutembacher

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syndrome have been seen since 1951. These cases were among 86 patients having interatrial septal defects both as an isolated lesion or associated with other anomalies. We may add that as a result of the experience with the above six cases, we feel that open corrective surgery for Lutembacher syndrome should be recommended.

Some divergence of opinion is still apparent among various authors as to what lesions this syndrome should embrace. There is agreement that an insignificant valve incompetent foramen ovale added to a mitral stenosis, or the presence of thickened mitral cusps in a case of true interatrial septal defect, or the existence of functional mitral incompetence in an instance of septum primum defect, should not be branded as Lutembacher syndrome. However, some authors, while they include any kind of significant interatrial septal defect as a part of the syndrome, confine the mitral lesion solely to stenosis.[9] Others like Donzelot[11] accept insufficiency as well as stenosis, both pure or mixed, as a component of the syndrome. It is difficult to conceive how one could get away from mixed lesions in these cases. The difference of approach may have accounted for some of the divergence in the reports about the incidence of the condition.

Another debated question regarding this syndrome is the effect of the one lesion over the prognosis of the other. Although the majority of cases behave in a manner as McGinn and White[2] concluded, namely, that the combination of these lesions reduces the average span of life as compared to the effect of either of them alone, the literature abounds with case reports since the time of Firket[3] (whose case was 74) where patients lived a long and normal span without significant disability for the most part. Rosenthal[12] reported a case of a woman 81 years old who lived a normal life with six pregnancies and had no discomfort related to her disease up to her 75th year. On autopsy examination she had severe stenosis of the mitral valve and an interatrial septal defect measuring 2 cm in cross diameter. He adds: "How such combination of lesions both of which may be of a severe degree can allow such a long and useful life is ill understood." Some explanation can be offered from hemodynamic considerations.

Hemodynamics

Pressure recordings made from normal human left and right atria reveal a somewhat higher pressure in the left atrium during most of the cardiac cycle except for a brief period at the beginning of the atrial filling.[13] The presence of the interatrial septal defect reduces this pressure difference between the atria to a slight degree, but still maintains the left to right gradient.[14] The superimposition of mitral stenosis on the interatrial septal defect has been shown by Calazel *et al.*[15] to increase this gradient. They also found higher values for shunt flows in these cases. Hyman[16] studied 41 patients of interatrial septal defect by cardiac catheterization, one-third of whom had superimposed mitral stenosis. The pressures recorded in the left atrium in cases complicated with mitral stenosis were no higher than the cases with interatrial septal defects alone. In our laboratory we have encountered an elevated pulmonary capillary or wedge pressure in cases of Lutembacher syndrome. Data on two of such cases are given in Table I.

Various explanations have been offered to account for a higher pressure in the left atrium as compared to the right. Hochrein *et al.*[17] proposed that the right atrium has a bigger cavity and can stretch to accommodate a larger volume as compared to the left, and hence with a similar volume of fluid contained, pressure on the right side would be lower. Little[18] isolated dog hearts intact with pulmonary veins and the venae cavae and measured the distensibility of the right and the left atrial systems. The right atrial system had twice as much initial filling volume as compared to the left and the volume elasticity curves indicated the right atrial system to be more distensible than the left for equal increments of volume. Barger *et al.*[19] theorized that the right side of the heart, on account of the 3 cusps in the right atrioventricular valve as compared to two on the left side, was able to achieve better ventricular filling. Cournand[20] explained that a little earlier contraction of the right atrium as compared to the left would, by transmission of the elevated pressure through the septal defect, cause a higher initial stretching of the left atrium and build up a higher pressure. Similar evidence is available

TABLE I

Hemodynamic Data on Two Cases of Lutembacher Syndrome

	Case 1. E. F. 41 F		Case 2. H. E. 49 F	
	Pressures (mm Hg)	O_2 contents (vol %)	Pressures (mm Hg)	O_2 contents (vol %)
Right atrium	15/3	14.05	5/2	9.8
Right ventricle	37/7	13.27	33/2	10.98
Pulmonary artery	40/10	13.12	28/10	10.02
Pulmonary capillary	22/7	14.97	23/10	—
Brachial artery	145/75	14.37	105/60	15.02
Cardiac output at rest:	5.9 l/min		3.1 l/min	
Arterial blood O_2 saturation:	94.4 per cent		94.1 per cent	

from experimental work of Brecher and Opdyke.[21] These authors demonstrated a diminution of the left-to-right pressure gradient, just before the atrial systole. Greatly reduced intrathoracic pressure produced by an inspiration of dyspneic type was shown to exaggerate the above-mentioned effects. Bayer[22] in 1951 suggested that because the left ventricle has a more muscular and less elastic wall than the right the left atrium has to build up a higher pressure to push on the blood.

Most of the above-mentioned factors probably act together to cause a pressure higher in the left than in the right atrium. Such higher pressure on the left side and the size of the septal defect do play a role in determining the size of the left to right shunt and, further, such a shunt can be conceived as a self-accelerating system by setting up a vicious circle of increased filling of the pulmonary circulation and left atrium. Yet there is conclusive evidence available that other factors more important than these exist to determine the magnitude of shunt flows. It is difficult to imagine that the pressure gradients of that small order between the atria could account for perpetuation of such tremendously large shunt flows as are seen in cases of interatrial septal defects.

Cause of Flow Through the Interatrial Septal Defect

Uhley[23] in 1942 hypothesized that since the left atrium always lay at a higher level as compared to the right, gravity was responsible in maintaining the left to right shunt. This hypothesis was put to test by Brannon *et al.*[24] by studying three patients with interatrial septal defects in head down position, when the left atrium would be at a lower level. The authors noted no change in blood oxygen values and hence concluded that gravity was not responsible for the flow across the defect. Hull[25] attributed the cause of left-to-right flow to the greater cross-section area of the outflow valve of the right atrium (50 to 75 per cent larger) and a longer and narrower inflow tract of the left ventricle with its thicker walls and greater resistance to stretch.

Little *et al.*[26] studied the dynamics of experimental interatrial septal defect in dogs. A higher pressure persisted in the left atrium in intact hearts through the entire cardiac cycle except for a brief period just before the atrial systole. Following the experimental production of a shunt, the left-to-right pressure gradient decreased a little on account of an increase observed in the right atrial pressure. Further, the effect on hemodynamics of various degrees of circulatory loading and the size of the defect were studied. While in small-sized defects, with rapid intravenous infusion, the left atrial pressure remained high in most instances, in cases of larger defects it fluctuated on both sides. Thus in case of small shunt flows, the increased amount of fluid is handled by the right ventricle with no change in its pressure by increasing its output, and it is reflected as increase in left atrial pressure. The effect of ventricular asys-

tole on atrial dynamics was extremely noteworthy. During asystole the atria behaved as a single chamber with equalized pressure; the left-to-right pressure gradient establishing itself again with resumption of the ventricular beat. However, according to these authors, elastic properties of the ventricles play only a minor role in the dynamics of the atria, because the greatest pressure gradient between the atria occurred at the so-called "V point" of atrial curves, at which time they are shut off from the ventricles and, further, significant difference could not be established regarding distensibility of the two ventricles. They concluded that the lesser distensibility of the left atrium and inincrease in right ventricular output were primarily responsible for maintenance of this pressure gradient. If this were true, then superimposition of mitral stenosis would not particularly affect the shunt flow in interatrial septal defect, although it may further reduce the systemic output in severe cases.

McCord, Komesu and Blount[27] in 1953 held that pressure relationships in the two atria were a reflection of the distensibility of the two ventricles. Since giant "a" waves were seen in right atrial curves in cases with hypertrophied right ventricles, the authors agreed that the right atrium had to hypertrophy in order to achieve effective filling of the less elastic hypertrophied right ventricle. In the light of above findings, the possible beneficial effects of the components of Lutembacher syndrome on each other may be discussed.

Effect of Interatrial Septal Defect on Mitral Stenosis

Firket[28] was the first one to say that interatrial septal defects would have a favorable effect on hemodynamics of mitral stenosis. The left to right shunt prevents an overloading of the left atrium due to mitral stenosis. The entire elastic and easily stretchable system constituted by the right atrium and great veins along with the liver, becomes available to the left atrium as an overflow mechanism. Hence, in these cases, unlike pure mitral stenosis, the embarrassment of the left atrium does not ensue unless the above mentioned stores are exhausted. The exception is in late cases of this syndrome where advanced right ventricular hypertrophy creates an opposing barrier for such left to right overflow. For this reason the episodes of pulmonary edema and left ventricular failure that are characteristically interspersed in the later course of isolated mitral stenosis are considerably delayed and quite rare in adults with Lutembacher syndrome. For the same reason congestion of pulmonary veins and capillaries is avoided. Hence certain other complications of mitral stenosis that depend on a high pulmonary venous pressure, like dyspnea, hemoptysis, and early increment of pulmonary arteriolar resistance are all delayed.[29] In fact if pulmonary arteriolar hypertension does develop on account of the septal defect in these cases, it protects the pulmonary veins and capillaries from the hypertrophied right ventricle, thus avoiding dangerously high pressures and development of pulmonary edema.[30]

The one hemodynamic complication of mitral stenosis which is aggravated by atrial septal defect is, of course, low systemic output. With the onset of pulmonary hypertension and right ventricular hypertrophy and consequent decrease in left-to-right shunt, the systemic output sometimes improves.

Effect of Mitral Stenosis on Atrial Septal Defect

It is more difficult to prove and imagine that mitral stenosis should have any beneficial effect on the course of an interatrial septal defect. From what has been said before, it is clear that in most cases of interatrial septal defect a small reversed shunt exists for a brief period of each cardiac cycle. This may not be significant under normal situations. Yet multiple conditions that temporarily raise the right atrial pressure, like crying and coughing in a baby, lung infections, asthmatic or dyspneic breathing, may all cause considerable reversal of shunt and cyanosis. Such reversal becomes more prone to occur after right atrial pressure goes up secondary to right ventricular hypertrophy.

Selzer and Lewis[31] have described 11 cases out of 180 isolated interatrial septal defects who had cyanosis, polycythemia, and clubbed fingers, yet had no pulmonary hypertension nor a single atrium. They explained it on the basis that the blood flow from the vena cava comes to

the heart in that phase of the heart cycle when there exists a reversal in the normal left-to-right pressure gradient between the atria. This has been amply confirmed by dye dilution curves by Swan *et al.*[32] and supported by others.[5] With mitral stenosis superimposed on the interatrial septal defect all such reversals of the normal gradient would be less likely to occur on account of a higher pressure in the left atrium maintained by the stenotic outlet. This would tend to decrease the chances of desaturation of arterial blood in which circumstance even a decreased systemic output would be somewhat better tolerated.

Summary

An attempt has been made to discuss the interplay of hemodynamic alterations that may result from superimposition of mitral stenosis and interatrial septal defect upon each other. It is concluded that there are reasons to believe on a hemodynamic basis that one lesion could possibly exert a beneficial influence over the other. These factors are possibly responsible for an occasional case of this syndrome having a surprisingly long and normal asymptomatic life.

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Some Physiologic Features of Atrial Septal Defect

Observations in 38 Adult Patients*

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THE APPLICATION of hypothermia to certain cardiac surgical problems has made possible the repair of atrial septal defects in the adult with an operative mortality of less than 10 per cent.[1] Using the hypothermia technic, open atrial septal defect repair has been achieved in a group of 38 adult patients. These patients ranged in age from 16 to 61 years and of the total group, 20 have been restudied following the operation.

Each patient was examined preoperatively to confirm or deny the clinical diagnosis of atrial septal defect by roentgen, electrocardiographic, and catheterization methods. Only patients in whom the diagnosis was confirmed at operation are included in this report. The data thus are not confused by the inclusion of malformations that may closely imitate atrial septal defect, such as partial anomalous pulmonary venous return to the right atrium, aortic sinus aneurysm with rupture into the right atrium, ventricular septal defect with tricuspid incompetence, or atrioventricularis communis defects. Of the total group, only two of the atrial defects were of the ostium primum variety and in only two instances was significant mitral valvular disease also present.

METHODS

The methods used in studying these patients have been the standard procedures. Angiocardiography has not been used regularly in this group and in the cases to be presented indicator dilution curves have not been extensively employed. Recently, indicator dilution curves utilizing Renografin† or human serum albumin made radioactive with I^{131} as a tracer isotope have been included in the routine studies but thus far have not, for practical purposes, been of great value. Manometric analysis of the blood samples taken at the time of heart catheterization has been carried out.

It should be emphasized at the outset that considerable error is involved in the application of the Fick law to the calculation of volume flow in either the systemic or pulmonary circulation and especially so in the presence of large left-to-right shunts.[2] It is well known that mixing of blood within the right side of the heart is not perfect, especially in the right atrium but also in the right ventricle and pulmonary artery. It is therefore unlikely that any single pulmonary artery blood sample represents a true mixed venous sample. The same type of sampling error is involved in drawing blood from any systemic artery although the variation in such samples is smaller than in the pulmonary circuit.

In calculating systemic blood flow in the presence of a left-to-right shunt, it is necessary to use the venous sample in the chamber proximal to the shunt as the mixed venous sample. In the case of atrial septal defect, this would be either vena cava or, if possible, an average value from both venae cavae. Since volume flow and blood

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oxygen content in the two venae cavae are not identical, average values may involve considerable error.[3] Probably the errors inherent in measuring oxygen uptake are inconsequential as compared to those related to blood sampling. All of these values are used in the calculation of both systemic and pulmonary blood flow by the Fick principle and obviously the results of such computations must be considered as estimates only. It is only fair to point out that any clinical method for calculating blood flow is far from perfect and that fundamental problems exist relative to indicator dilution,[4] arterial pulse contour,[5] and other methods.

Preoperative Observations

Measurements have been made of systemic and pulmonary blood flow, pulmonary arterial pressure, systemic arterial saturation, oxygen uptake, etc. Volume flow in both circuits, total pulmonary vascular resistance, and, in a small number of cases, the right ventricular pressure work have been calculated. The pertinent data are given in Table I.

TABLE I

Preoperative Values in 38 Cases of Atrial Septal Defect

Measurement	Maximum	Minimum	Average
Systemic flow (L/min)	9.5	2.2	4.6
Pulmonary flow (L/min)	34.0	5.2	17.2
Left-to-right shunt (L/min)	30.9	1.6	12.6
Pulmonary artery pressure (mm Hg)	82/37	12/4	40/16
Pulmonary artery mean pressure	62	7	24
Pulmonary resistance (dynes cm^{-5} sec)	948	33	160
Oxygen capacity (vol %)	24.5	13.3	18.4
Oxygen consumption (ml/min)	443	149	250
Femoral blood O_2 saturation (%)	102	93	97
Pulmonary blood O_2 saturation (%)	95	68	89
Left atrial blood O_2 saturation (%) (9 cases)	100	94	98
Left atrial pressure (mm Hg) (9 cases)	20	2	8
Right ventricular pressure work (kg m/hr) (13 cases)	688	96	387

Systemic Flow: In order to calculate systemic blood flow it is necessary to know the oxygen uptake, the oxygen content of a mixed venous sample proximal to the shunt, and the oxygen content of the pulmonary venous blood which, in the normally saturated patient without a right to left shunt, is assumed to be the same as the oxygen content of blood in any systemic artery. No patient in this group had a systemic blood oxygen saturation of less than 93 per cent, which is at the extreme lower limit of normal. The mixed venous blood oxygen contents covered a wide range so that the arteriovenous difference fell within the limits of 8.1 and 3.1 vol %. In the entire group of 38 patients, the oxygen uptake ranged between 149 and 443 ml/min with an average value of 250 ml/min. Using these data, the average systemic blood flow prior to operation was 4.6 L/min, a normal value.

Pulmonary Blood Flow: In certain cases the pulmonary artery blood oxygen content was so similar to the systemic artery blood oxygen content that for practical purposes they could be considered identical. The error in this laboratory in doing duplicate oxygen contents on a single sample of blood by the Van Slyke and Neill method is about 0.2 vol %. In four patients in this series, the arteriovenous oxygen difference between pulmonary and systemic arterial blood was 0.5 vol % or less. Arbitrarily, the data from those patients have not been included because they would have made the pulmonary blood flow values erroneously high. With those patients excluded, the pulmonary blood flow varied between 34.0 and 5.2 L/min, the minimum flow occurring in a patient with marked elevation of the pulmonary artery pressure in the absence of mitral valve disease. The average value for the group was 17.2 L/min or about four times the systemic blood flow.

Left to Right Shunt: The difference between the systemic and pulmonary blood flow is the amount of blood being shunted from left to right at the atrial level. The range of values was between 1.6 and 30.9 L/min, the average

being 12.6 L/min or about three times the systemic blood flow. This is not an entirely correct estimate since it has been well demonstrated by indicator dilution technics that right to left flow does occur in uncomplicated atrial septal defects with normal pressures although the volume of the right to left shunt is ordinarily not large enough to be picked up by oxygen content studies alone.[6]

Pulmonary Artery Pressure: The measurement of pressure at the time of heart catheterization seems to be reasonably accurate and the figures obtained may be considered as approximately correct. In this series, the pressure records were made using a strain gauge and a direct writing recorder. The system was critically damped. The baseline for measuring all pressures was the midpoint of the right atrium which cannot be located precisely in each patient but which may be assumed to be 10 cm anterior to the posterior body surface. The mean arterial pressure was derived by electronic integration of the pressure curve.

In terms of conventional systolic and diastolic readings, the pulmonary artery pressure covered a wide range, varying from a low of 12/4 mm Hg to a high of 82/37 mm Hg. Eight patients had moderately severe pulmonary hypertension, their readings being 82/37, 72/34, 80/42, 75/27, 70/23, 81/35, 75/38, and 53/16 mm Hg. Only two of the eight patients had coexisting mitral valve disease. The average pressure was 40/16 mm.

It should be mentioned that probably higher pulmonary artery pressures do occur in atrial septal defect but persons in whom this was believed to occur were not submitted to operation and hence are not included in this report.

Of more practical value is the mean pressure obtained by integration of the pressure curve. The mean pulmonary artery pressure in this group ranged from 7 to 62 mm Hg with an average value of 24 mm Hg. Since the normal pulmonary artery pressure in this laboratory is 25/10 plus or minus 5 mm Hg and since the normal mean pulmonary artery pressure is about 15 mm Hg, it is evident that this group of patients had, on the average, only mild pulmonary hypertension, excluding the eight patients mentioned earlier.

Total Pulmonary Vascular Resistance: Pulmonary artery pressure depends on the volume flow through the pulmonary arterial system and the resistance to flow through that system. Resistance is determined by many factors including the cross-sectional area of the pulmonary arteriolar bed, blood viscosity, and impedance imposed by the mitral valve. If the left atrial pressure is measured, the factor of mitral valve impedance can be removed from the equation but in the absence of regular measurement of left atrial pressure, the value computed is total pulmonary vascular resistance rather than pulmonary arteriolar resistance. The relationship can be expressed as:

$$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$$

The normal value for total pulmonary vascular resistance is about 250 dynes cm^{-5} sec. In this series of patients the total pulmonary vascular resistance varied from a low of 33 to a high of 948 dynes cm^{-5} sec and the three highest values were 332, 543, and 948 dynes cm^{-5} sec occurring in patients without associated mitral valve disease. Those patients were 32, 51, and 19 years of age, respectively. In this small sample the level of total pulmonary vascular resistance was not related to age or hence to the duration of increased pulmonary blood flow. The average value was 160 dynes cm^{-5} sec, somewhat below normal for an adult.

Left Atrial Pressure: On nine occasions it was possible to cross the atrial septal defect and measure the left atrial pressure. The pressure ranged between 2 and 20 mm Hg, the highest reading occurring in a patient who also had mitral incompetence. In three instances it was not possible to measure a mean pressure gradient across the atrial defect, suggesting that flow occurred as a result of phasic differences in pressure rather than a higher mean pressure in the left atrium. In the remaining patients, the mean pressure gradient across the septal defect was from 1 to 10 mm Hg.

Left Atrial Blood Oxygen Saturation: In the same nine cases mentioned above, blood samples were drawn from the left atrium. The oxygen saturation of the samples fell between 94 and 100 per cent, the average being 98 per cent.

Miscellaneous Preoperative Observations: Other measurements of less importance than those thus far described are also given in Table I.

Postoperative Observations

Studies similar to those done preoperatively were carried out in 20 patients after surgery. Postoperative values and their alterations as compared to preoperative findings are given in Table II.

TABLE II

Postoperative Values in 20 Cases of Atrial Septal Defect

Measurement	Maximum	Minimum	Average	Preoperative average	Change in average value
Systemic flow (L/min)	10.1	2.8	6.1	4.6	+ 1.5
Pulmonary artery pressure (mm Hg)	80/29	7/1	26/10	40/16	− 14/6
Pulmonary artery, mean pressure	49	3	16	24	− 8
Pulmonary resistance (dynes cm^{-5} sec)	687	49	240	160	+ 80
Oxygen capacity (vol %)	22.2	15.3	17.8	18.4	− 0.6
Oxygen consumption (ml/min)	313	163	213	250	− 37
Femoral blood O_2 saturation (%)	103	92	98	97	+ 1
Pulmonary blood O_2 saturation (%)	87	71	79	89	− 10
A-V O_2 difference (vol %)	6.5	2.5	3.7	5.2	− 1.5
Right ventricular pressure work (kg m/hr) (13 cases)	213	39	98	387	−289

Systemic Flow, Pulmonary Flow, and Left to Right Shunt: In only one patient was a residual left to right shunt found, this occurring through an anomalous pulmonary vein that entered the right atrium at its junction with the superior vena cava. This had not been discovered at the time of operation and consequently had not been corrected. The catheter entered the anomalous vein at the time of the postoperative catheterization. The residual shunt in this case was calculated to be 2.1 L/min as compared to 8.7 L/min preoperatively. For the entire group, the systemic flow was found to be 6.1 L/min, a value 1.5 L/min larger than preoperatively.

Pulmonary Artery Pressure: The pulmonary artery pressure was found to average 26/10 mm Hg postoperatively with an average mean pulmonary artery pressure of 16 mm Hg. Three of the eight patients previously mentioned whose pressures were the highest preoperatively were studied after operation. In one case the preoperative value of 53/16 mm Hg became 75/30 and the mean pressure changed from 30 to 49 mm Hg. This patient had mitral stenosis at the time of operation and this was unfortunately converted to mitral incompetence. A second case had a pressure of 82/37 before operation and 80/29 mm Hg after surgery. In this instance mitral incompetence was present before the operation and was not corrected by the operation. In a third patient the initial pulmonary artery pressure was 72/34 mm Hg. It was not possible to enter the pulmonary artery at the second heart catheterization but the right ventricular pressure after operation was 28/4 mm Hg. In this case the original pulmonary hypertension seems to have been caused solely by the increased pulmonary blood flow without anatomic change in the pulmonary arteriolar bed. A functional decrease in the size of the pulmonary arterioles cannot, of course, be excluded.

One other pressure change noted in the preoperative material and not fully understood until the postoperative studies had been done was related to the presence of a systolic gradient across the pulmonary valve. At first glance these data suggested that mild pulmonary stenosis was also present since the systolic gradient in

six cases ranged from 12 to 28 mm Hg. Following obliteration of the left to right shunt, no systolic gradient higher than 5 mm Hg was found, indicating that organic pulmonary stenosis had not been present. It seemed reasonable to call this "relative" pulmonary stenosis based upon increased volume flow across an anatomically normal pulmonary valve. In this series, no case of true pulmonary stenosis was found. This phenomenon is probably responsible for other cases reported in the literature as atrial septal defect with pulmonary stenosis in which gradients across the pulmonary valve as low as 15 mm Hg were measured.[7]

Total Pulmonary Vascular Resistance: A regular increase in the total pulmonary vascular resistance was seen following operation. The values ranged from 49 to 687 dynes cm^{-5} sec with an average value of 240 dynes cm^{-5} sec. This change was related not so much to changes in pressure but rather to the marked change in pulmonary blood flow. It is interesting to consider that this change is also related to the oxygen tension in the pulmonary artery blood since it has been shown that increasing the pO_2 is accompanied by a drop in pulmonary vascular resistance while a decrease in the pO_2 is followed by a rise in the resistance.[8] The preoperative and postoperative values for pulmonary artery blood oxygen saturation (89 and 79 per cent, respectively) imply similar changes in the pO_2 and would fit with this concept. The patient with an atrial septal defect would seem to be similar physiologically in some respects to a person breathing high oxygen concentrations.

Right Ventricular Pressure Work: One of the earlier reports on the dynamics of atrial septal defect in the adult included measurement of the right ventricular pressure work. In the series reported, the right ventricular pressure work averaged 361 kg m/hr as compared to a theoretical normal value of 105 kg m/hr. It was also pointed out that these calculations ignored the factors of kinetic work and of work resulting from turbulent flow.[9]

The right ventricular pressure work was calculated both before and after surgery in 13 subjects. The relationship of pressure, flow, and work is as follows:

Right ventricular pressure work = 60 Q times R (0.0135)

where

Q = pulmonary blood flow in L/min
and R = right ventricular mean systolic pressure in mm Hg.[9]

Preoperatively, the average value for right ventricular pressure work was 387 kg m/hr while following surgery the average value was 98 kg m/hr. The initial value corresponds closely to that previously reported and is definitely above normal while the postoperative value is well within normal limits. As with total pulmonary vascular resistance, the major contributing factor to this change was the marked reduction in pulmonary blood flow rather than a sizeable change in pressure. The right ventricular mean systolic pressure dropped only from 28 to 17 mm Hg while the decrease in right ventricular pressure work was proportionately much larger.

Discussion

The data obtained in this group of patients outline the major physiologic abnormalities in atrial septal defect in the adult, which include enormous increases in pulmonary blood flow, only mild to moderate increases in pulmonary artery pressure, lower than normal values for total pulmonary vascular resistance, and normal systemic arterial blood oxygen saturation. These findings are in agreement with other data in the literature although individual exceptions to the general hemodynamic pattern do occur.[10] The studies were not done in such a manner that the presence of small right to left shunts despite normal pulmonary artery pressure could be either confirmed or denied but in any event such shunts, if present, were not large enough to alter the systemic arterial blood oxygen saturation. Closure of the atrial septal defect brought about the changes that one would anticipate such as reduction of pulmonary blood flow to normal, reduction of pulmonary artery pressure if it was initially elevated, and a return of the total pulmonary vascular resistance towards normal. Changes in the functions of lesser importance, as enumerated in Tables I and II, were not of real significance and do not merit further discussion here.

Genesis of Pulmonary Hypertension: One question of major importance concerns the genesis of pulmonary hypertension in atrial septal defect

since major elevations of pulmonary artery pressure make surgical repair impossible. The lung vascular bed ordinarily can accept tremendous increases in blood flow, as has been shown in this series of cases, and as a rule the pulmonary artery pressure is only slightly elevated in atrial septal defect. All of the factors contributing to the development of pulmonary hypertension in rare cases have not been defined. That long standing left to right shunts may be complicated by the development of pulmonary hypertension is suggested by clinical experience and can be produced in the dog under certain circumstances.[11] Anatomic alteration of the media and the intima of the pulmonary arterioles can be seen in the experimental animal. This is not always the course of events in the human with atrial septal defect with pulmonary hypertension since the patient in this group with the highest pressure was 19 years old, had a normal pulmonary capillary pressure, and a normal lung biopsy, with no evidence of pulmonary arteriolar sclerosis. Such a finding immediately raises the question of "spasm" of pulmonary arterioles and hence an increase in vascular resistance but there seems to be no other evidence to support such an idea.

Another possible explanation for the pulmonary hypertension is that it has not developed over the years but has been present since birth, representing a residual of the normal fetal pulmonary hypertension. Such a possibility cannot be ruled out with certainty but personal experience with atrial defect in children would suggest that this is not a likely explanation.

Probably a common contributing cause to pulmonary hypertension in the adult with atrial septal defect is the coexistence of mitral valve disease, either stenosis or incompetence. The incidence of this combination of abnormalities is given as about 6 per cent[12] and played a significant role in two of the patients in this series. In one patient who had mitral stenosis, mitral incompetence was produced at operation and the mean pulmonary artery pressure rose from 30 to 49 mm despite closure of the atrial defect. The net result, however, was a reduction of the right ventricular pressure work from 604 to 213 kg m/hr, so that the patient was improved functionally. In the second case, mitral incompetence was present before surgery and despite closure of the septal defect, the pulmonary artery pressure remained at the high preoperative level. The pulmonary capillary pressure after operation was 19 mm Hg, indicating to some degree the part played by the mitral valve disease in keeping the pulmonary artery pressure elevated.

Finally, statistical methods have not been used in the evaluation of these data other than simple averages for the reasons that the total sample is small and the accuracy of the basic observations, especially blood flow measurements, would not warrant precise statistical manipulations. Even the use of averages may be questioned. Claude Bernard expressed it thus: "Another very frequent application of mathematics to biology is the use of averages which, in medicine and physiology, leads, so to speak, necessarily to error. There are doubtless several reasons for this; but the greatest obstacle to applying calculation to physiological phenomena is still, at bottom, the excessive complexity which prevents their being definite and comparable one with another. By destroying the biological character of phenomena, the use of averages in physiology and medicine usually gives only apparent accuracy to the results."[13]

Summary

(1) Thirty-eight adult patients with atrial septal defect have been studied before operation, and 20 have been restudied postoperatively.

(2) Of the group, two had significant mitral valve disease and two were of the ostium primum type although they could not be separated from the secundum defects by their hemodynamic findings.

(3) The major physiologic findings before operation were: (a) marked increase in pulmonary blood flow; (b) normal systemic blood flow; (c) mild elevation of pulmonary artery pressure; (d) lower than normal total pulmonary vascular resistance; (e) increased right ventricular pressure work; (f) normal systemic arterial blood oxygen saturation.

(4) Surgical correction of the atrial septal defect resulted in a reversion of the physiologic abnormalities towards or to normal.

(5) "Relative" pulmonary stenosis may be

present in the face of marked increases in the pulmonary blood flow.

(6) The genesis of pulmonary hypertension in certain cases is not totally understood but may be related to: (a) pulmonary arteriolar sclerosis; (b) residual fetal pulmonary hypertension; (c) associated mitral valve disease; (d) "spasm" of the pulmonary arterioles.

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The Electrocardiogram in Interatrial Septal Defects*

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THE electrocardiogram has been, in the last few years, one of the most important factors in the diagnosis of congenital heart disease. The studies performed by the Mexican school of cardiology, particularly by Sodi-Pallares[1] and Cabrera,[2] have shown that in many cases the diagnosis of the malformation may be suggested by an accurate analysis of the graphic records.

As a matter of fact, the electrocardiogram does not show the anatomic lesions as such. However, they may be suspected through the overloading of the cardiac chambers as demonstrated in the tracings. Atrial septal defects present some particular electrocardiographic patterns which, although not pathognomonic, yet are very suggestive of the diagnosis.

For many years the appearance of a right bundle branch block pattern in a patient with congenital heart disease has been suggestive of an interatrial septal defect. This pattern is characterized by wide S waves in lead 1, a late R in aVR, and rsR′ or rsR′s′ in leads V_3R and V_1, extending sometimes to V_2. This morphology has been pointed out by Monroy and Cabrera[3] as representing diastolic overloading of the right ventricle. In a previous paper[4] we have discussed the significance of this pattern, and correlated it with the magnitude of the shunt flow through the atrial defect.

DESCRIPTION OF ECG FINDINGS

Actually, the electrocardiographic alterations in patients with uncomplicated interauricular septal defects are essentially related to increase in blood volume and work for the right ventricle without any significant change in pressures.[5] The most common findings seen in the records in these malformations are as follows:

(1) *P Wave and P Vector:* The P wave may or may not be normal. When the size of the defect is large enough to produce significant overloading of the right atrium, one can see peaked P waves in the right precordial leads (Fig. 1).

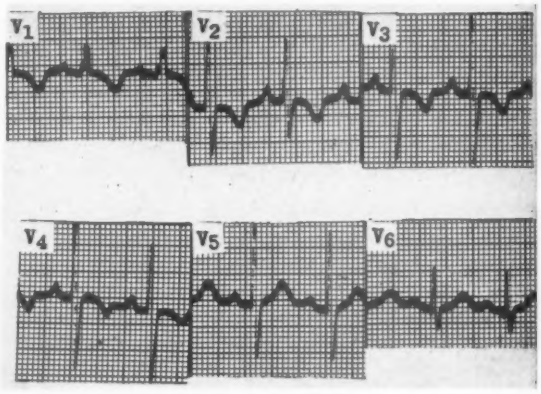

Fig. 1. Peaked P waves in the right precordial leads in a patient with a large atrial septal defect.

In these cases generally there also exists a tendency of the auricular vector to deviate to the right although not usually exceeding plus 80°. This is sometimes helpful in the differential diagnosis from the so-called "P pulmonale," which one sees in chronic emphysema of the lungs or in cases of pulmonary emboli. In these conditions the P vector is markedly deviated to the right, generally exceeding plus 90°. In a few cases the P axis may show left deviation (beyond plus 20°). This is more commonly

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found when there is associated left auricular overloading as in Lutembacher's syndrome.

(2) *P-R Interval:* Although it has been stressed by several authors[6] that increase in duration of the auricular-ventricular conduction is a common finding in atrial septal defects, we have seen this only when the defects are very large or else when they are located in such a particular position as to involve the conduction system, as one sees in cases of ostium primum.

tants of Bailey, that is ranging from −60° to −150°. This is most generally seen when there exists a defect type A-V communis or ostium primum with mitral insufficiency[7] (Fig. 2).

(4) *QRS Complex:* One of the most characteristic and frequent findings in the electrocardiograms of patients with atrial septal defects is the presence of R′ or R′s′ waves in right precordial leads, particularly in V_1 and V_3R (Fig. 3).

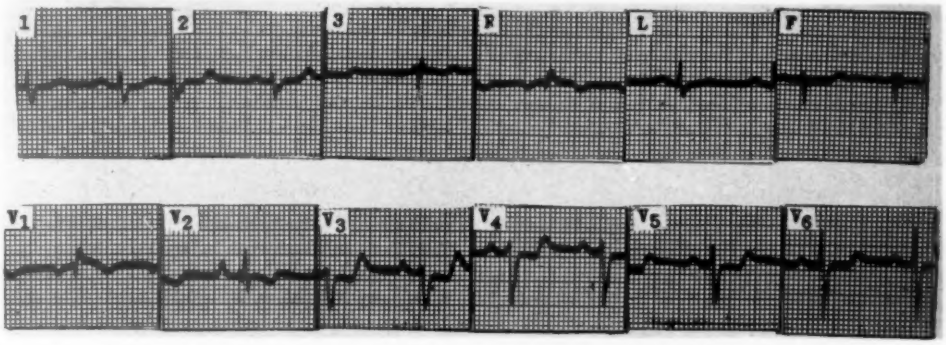

Fig. 2. Interauricular septal defect, type ostium primum—$_A$QRS = −110°.

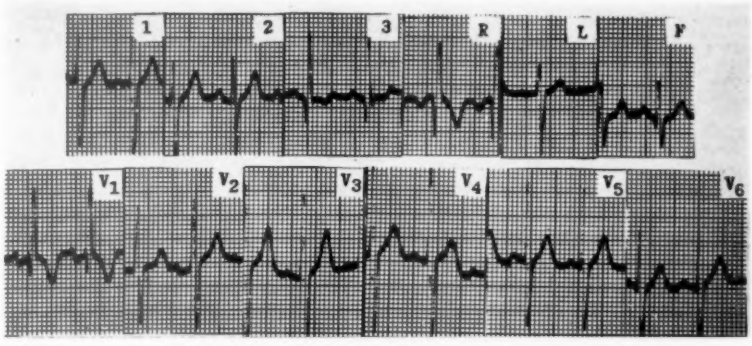

Fig. 3. rsR′ pattern in lead V_1 in a case of atrial septal defect.

(3) *Mean Ventricular Vector:* In our own experience the mean QRS vector lies in the frontal plane between plus 75° and plus 135°, in the great majority of cases. In the horizontal plane, this vector may be oriented either backward or forward. In patients in which there is development of pulmonary hypertension, there is a tendency of this vector to deviate more and more to the right and anteriorly. In some cases the mean vector of ventricular activation may be found in the second or third sex-

Although we do not accept this morphology as strictly meaning diastolic overloading of the right ventricle, we admit that this pattern appears more frequently in those malformations which gives rise to that type of overloading, such as interatrial septal defects and anomalous pulmonary venous drainage. As we[4] and other authors[8] have stressed before, this morphology may also be found in other conditions as pulmonic stenosis and mitral lesions with pulmonary hypertension. In the same way, such a pattern

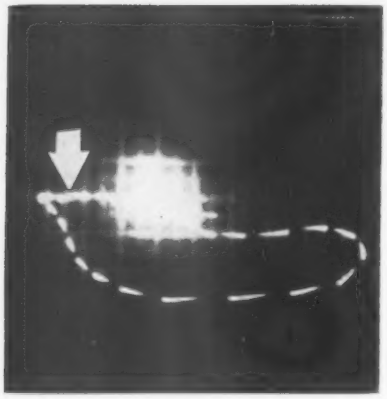

Fig. 4. Atrial septal defect—frontal vectorcardiogram showing delay in conduction in the terminal portion of the loop (arrow).

may appear in some cases of chest deformity which produce rotation of the heart, as for instance pectus excavatum.[9]

In our own experience this pattern (R′ or R′s′) has been found in lead V_1 in 80 per cent of patients with atrial septal defect, and it was never seen in cases with associated pulmonary hypertension. This morphology would appear to be related to a delay in conduction in the basal parts of the right ventricle, as a consequence to dilatation and hypertrophy of these regions.[10] This delay can be easily identified in the vectorcardiogram (Fig. 4).

In a few cases, on account of a marked rotation of the heart and generally associated with dilatation of the right atrium,[11] one sees a Q wave in V_1, the morphology in this lead being a qR or a qRs (Fig. 5).

Whenever pulmonary hypertension develops, with increase in pressures within the right ventricle, the so-called systolic right ventricular overloading pattern, i.e., tall slurred R waves, followed or not by ST-T changes, appears (Fig. 6). In such cases there no longer exists any predominant thickness or enlargement of the basal regions, the hypertrophy being of the concentric type.

Changes After Surgery: After the correction of the atrial septal defect, the following changes have been seen almost constantly in the electrocardiogram:

(a) Tendency of the P axis to deviate to the left and backward.

(b) Decreased right deviation of the aQRS in the frontal plane.

(c) Disappearance or decrease in voltage of the R′ or R′s′ pattern in lead V_1.

These changes may be explained by the reduction in the overloading of the right chambers after the closure of the defect.

Conclusions

We could conclude that although there is no pathognomonic electrocardiographic pattern for the diagnosis of interatrial septal defect, it may be strongly suspected in a large number of cases. Thus, in the presence of congenital heart disease, whenever there exists an R′ or R′s′ or less commonly a qR pattern in right precordial leads with right axis deviation, with or without peaked P waves in V_1 and V_2 and in the absence of any signs of associated left ventricular over-

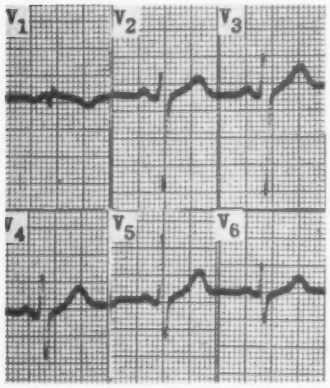

Fig. 5. Dilatation of the right atrium—Qr pattern in lead V_1.

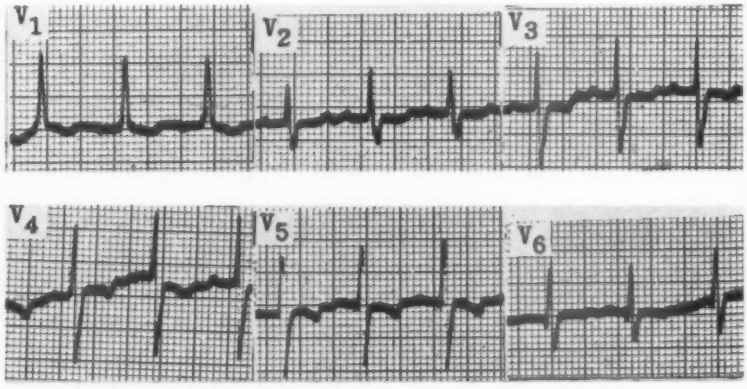

Fig. 6. The pattern of the so-called "right ventricular systolic overloading" in a case of atrial septal defect with marked pulmonary hypertension (pressure in pulmonary artery: 110/82 mm Hg).

loading, the possibility of an interatrial septal defect must be considered and other examinations as roentgenologic and hemodynamic studies must be carried out in order to establish the diagnosis.

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Atrial Septal Defect*

The Electrocardiogram and Its Hemodynamic Correlation in 100 Proved Cases

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ANATOMIC confirmation of the diagnosis in a considerable number of cases of congenital heart disease is now possible as the result of the recent introduction of technics for surgical repair of a variety of cardiac malformations. The anatomic diagnosis is necessary for critical evaluation of the diagnostic methods used to differentiate these conditions. For example, more precise evaluation of the electrocardiogram in proved cases has revealed differences of diagnostic significance between atrial septal defect and common atrioventricular canal.[1]

The present report consists of a detailed study of the electrocardiograms recorded in 100 cases of atrial septal defect proved and accurately described at the time of surgical correction. Included are cases of atrial septal defect in the usual location (fossa-ovalis type)[2] and cases in which anomalous connection of the right pulmonary veins is associated with interatrial communication. Excluded are cases of common atrioventricular canal[3] and cases of total anomalous pulmonary venous connection, certain examples of which are functionally and clinically identical to cases of atrial septal defect. The functional status of all these patients was evaluated preoperatively by cardiac catheterization.

MATERIAL AND METHODS

The series consisted of 71 females and 29 males; 28 patients were less than 16 years of age, and the total range was from $1^1/_2$ to 60 years (Table I).

In 87 of the 100 patients, the repair of the intracardiac defect was accomplished by use of the atrial well of Gross.[4] Closure in the remaining 13 patients was accomplished under direct vision, with use of total body perfusion[5] to support vital functions. Included in this latter group were several "high-risk" patients with intractable cardiac failure in whom the level of atrial pressure precluded use of the former technic. Almost all the patients in this series were operated on by one surgeon (Dr. J. W. Kirklin), who reported in detail on the external appearance of the heart and on the result of digital examination of the interior of the heart, including the size and location of the

TABLE I

Age Incidence and Average Duration of QRS in 100 Cases of Atrial Septal Defect

Age, years	Patients*	Mean duration of QRS, seconds	
		All patients	Excluding patients with complete bundle branch block
$1^1/_2$–10	13 (0)	0.085	0.085
11–20	16 (1)	0.096	0.095
21–30	24 (3)	0.096	0.093
31–40	18 (8)	0.108	0.094
41–50	22 (5)	0.102	0.094
51–60	7 (2)	0.110	0.102

* Figures in parentheses indicate number of patients in each group with complete right bundle branch block.

* From the Sections of Physiology and Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

interatrial communication, the structure and functional status of the atrioventricular valves, the interventricular septum, and the location of the atrial orifices of the pulmonary veins, the venae cavae, and the coronary sinus. The accuracy of the evaluation at the time of operation was confirmed in 10 cases in which necropsy findings were also available.

Cardiac catheterization,[6] including application of indicator-dilution technics,[7] was done at the Mayo Clinic on 96 of the patients and data from other laboratories were available in the remaining four patients. In 93 instances, data were sufficiently complete for the calculation of pulmonary and systemic blood flows and pulmonary and systemic "vascular resistances" (pressure-flow ratios). All data reported were obtained while the patients breathed room air.

The electrocardiograms were obtained with a sensitivity of 10 mm per millivolt for the standard leads and the augmented unipolar extremity leads;[8] this same sensitivity was used for most of the precordial leads, but in five patients the sensitivity for precordial leads was half of this value. Standard leads were used in all patients, and unipolar extremity leads were used in 84 patients. Precordial leads from positions V_1 to V_6 were used in 86 patients, while only V_1, V_3, and V_5 were recorded from the remaining 14. The majority of tracings were obtained by means of the Cambridge electrocardiograph. For the remainder, the Sanborn Viso-Cardiette was used. The magnitude of the deflections and the duration of the various waves were measured directly from the records. Correction to an "N" sensitivity was done when waves were measured in leads recorded with N/2 sensitivity. The electrocardiographic criteria used to evaluate the status of the right and left ventricles and the presence or absence of enlargement of the atria are those of the Mexican school of electrocardiography.[9]

Definitions and Normal Values

The term "overload"[10] rather than "hypertrophy" is used concerning the status of the ventricles, since this avoids use of a term that implies an anatomic alteration which may not necessarily be demonstrable. "Overload" has a functional connotation that may apply more appropriately to the hemodynamic factors basic to the electrocardiographic changes, as evident from studies such as those of Robb and Robb,[11] and Cabrera and Monroy.[12] The use of "overload" appears particularly rational in congenital malformations such as atrial septal defect, in which normal pulmonary arterial pressures are common, and a dilatation[13–16] rather than hypertrophy of the right ventricle is the usual finding.

The duration of the interval known as the "intrinsicoid deflection" of the QRS complex measured in the precordial leads is considered an important indication of the presence of ventricular overloads.[9,17] Sodi-Pallares[9] described the method for measurement of this interval but did not discuss its particular application to those complexes recorded from positions in which this measurement can be used to indicate the presence or absence of overloading of the right or left ventricle.

For evidence of *overloading of the right ventricle*, the duration of the intrinsicoid deflection is measured in V_1.[9,17–19] Kossman[17] stated that the maximal value in normal persons from 20 to 35 years of age is 0.033 sec. Ziegler,[18] studying 387 normal children aged 1 to 16 years, found this interval to be greater than 0.030 sec in only two instances; this shorter time (0.030 sec) is accepted as the maximal limit of normal by the Mexican authorities,[19] regardless of the age of the patient. On the basis of these data, duration of the intrinsicoid deflection in lead V_1 in excess of 0.030 sec when the duration of the QRS complex is less than 0.12 sec and in the absence of evidence of primary myocardial disease is regarded as evidence of overload of the right ventricle.

In the measurement of this interval over the left precordium, uncertainty may exist as to whether or not the recorded potentials represent activation of the left ventricle. Because the initial vectors[20] representing ventricular activation are directed from the left to the right ventricular chamber and are not perpendicular to the anatomic ventricular septum,[9] complexes similar to those recorded over the right ventricle normally are obtained from a region of the left ventricle adjacent to the ventricular septum. When enlargement of the right ventricle causes

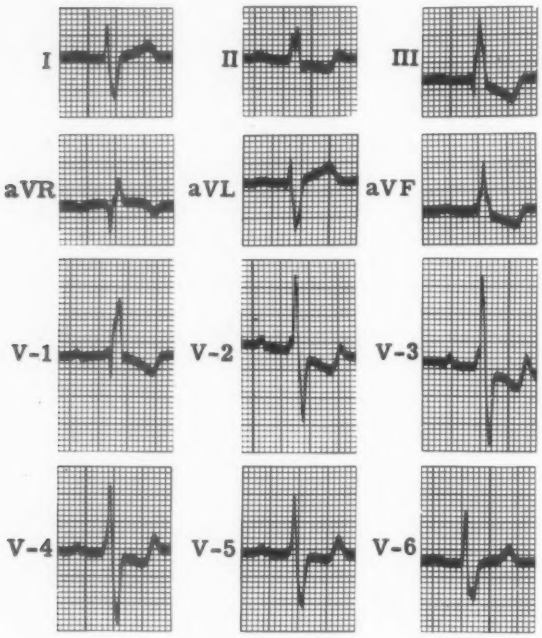

Fig. 1. (above) Tracings from a 50-year-old man obtained three days before hemodynamic studies of the circulation. Note the prolonged PR interval (seen in 16 per cent of the cases). Alterations of the P waves suggest enlargement of the left atrium. (The axis of the P wave in the horizontal plane is similar to that in Figure 7.) The isoelectric plane of the T wave intersected the precordium simultaneously in V_2, V_3, and V_4, indicating that the mean axis is parallel to the frontal plane. Hemodynamics: pulmonary arterial pressure = 75/30; pulmonary blood flow = 4.8 L/min/m². Surgical findings: defect (4 by 5 cm) in the middle of the atrial septum; normal mitral and tricuspid valves.

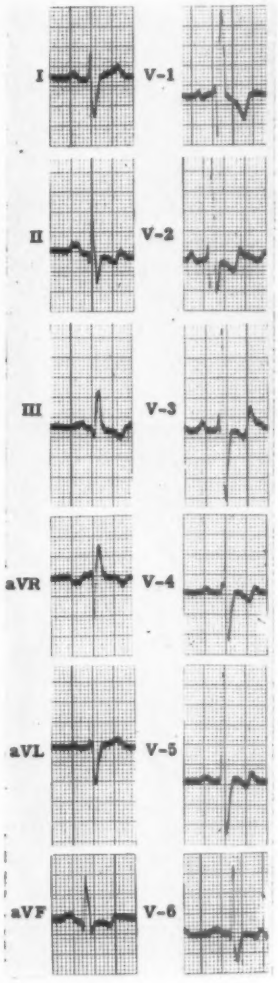

Fig. 2. (right) Tracings from a 33-year-old woman obtained three days before cardiac catheterization. Note alterations of the P wave indicative of enlargement of the left atrium. Complete right bundle branch block is associated with qRS in V_6. Observe the alterations of the ST segment and T wave, as seen in Figures 1, 7, and 9, and as found in 37 per cent of the cases. Hemodynamics: moderate increase of pulmonary arterial pressure (55/21); high pulmonary blood flow of 16 *l*/min/m². Surgical findings: constrictive pericarditis, with moderate atrial septal defect and tricuspid insufficiency.

clockwise rotation of the heart in the anatomic axis, the configuration RS may occur in V_5 and V_6. The certain identification of potentials truly representative of activity of the left ventricle is only possible when an initial q deflection is present in a left precordial lead. Furthermore, the presence of electric dominance of the right ventricle is unlikely to affect the duration of the intrinsicoid deflection in such leads. Therefore, the duration of the intrinsicoid deflection representative of activation of the left ventricle is measured in lead V_5 or V_6 only when an initial negative wave (q) can be identified. The values used to determine the duration of this interval were obtained in persons without cardiovascular abnormalities in whom an initial q deflection is a common finding in records taken over the left precordium.

The maximal normal duration of the intrinsicoid deflection of the QRS complex over the left precordium is 0.04 sec.[19] Ziegler[18] demonstrated that this interval is related to age, only 5.5 per cent of patients aged 6 months to 8 years having durations in excess of 0.035

sec. Therefore, values greater than this in patients up to eight years of age and values in excess of 0.040 sec for patients more than eight years of age are considered to indicate *overloading of the left ventricle.*

Electrocardiographic Findings

DISORDERS OF RHYTHM

Nine of the 100 patients had auricular fibrillation. Three patients showed multiple ventricular extrasystoles, and one showed evidence for multiple auricular ectopic foci.

PR INTERVAL

First degree atrioventricular block (Fig. 1) was present in 16 patients, one patient showing a Wenckebach phenomenon.[21] Three of these patients had shown evidence of digitalis effect. In 27 other patients, the PR interval was at the upper limit of normal for the rate and age[22] (Fig. 2); two of these patients showed electrocardiographic evidence of digitalis effect. The PR interval was normal in the remaining 57 patients.

P WAVE

Analysis and understanding of the wave representing auricular activation as detected electrocardiographically are greatly simplified by use of the concept of a loop representing the changes in direction and magnitude of the successive instantaneous mean electric axes, resulting from activation of this chamber. Use of this conceptual tool makes possible the prediction of the general configuration of P in any lead in a given plane from the appropriate loop and, conversely, the prediction of the loop from at least two leads in the corresponding plane.[23]

The mean electric axis bisects the loop of activation, and the distribution of this vector for the P wave in the frontal plane calculated from the three standard leads is given in Figure 3. In 90 per cent of our patients, the direction of this mean axis was between +20 and +80 degrees. Since the loop of the P wave in the frontal plane rotates counterclockwise,[24] the configuration of the P wave in each standard or unipolar extremity lead for each

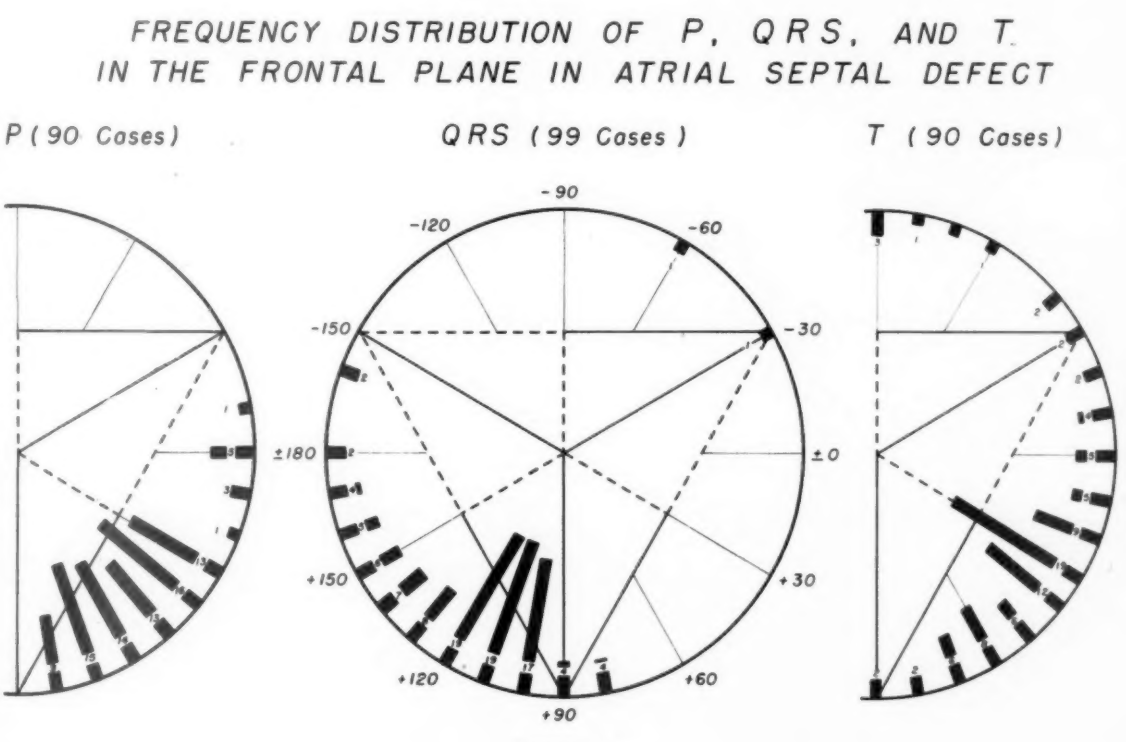

Figure 3.

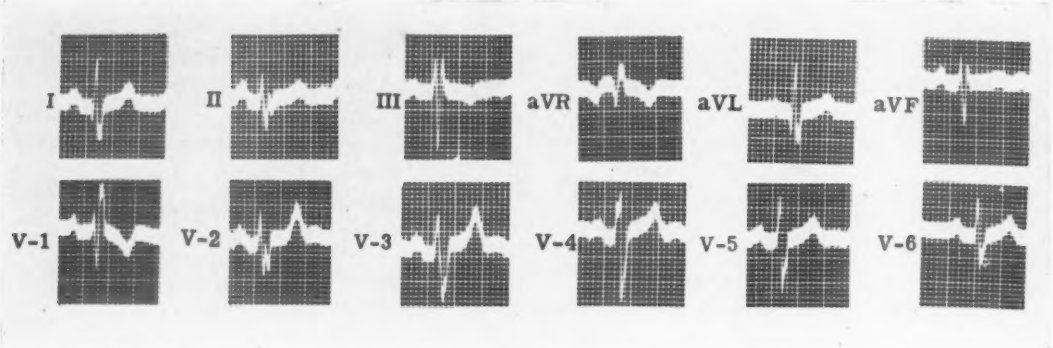

Fig. 4. Tracings from a 31-year-old woman obtained six days after cardiac catheterization, showing ventricular activation of the type described as suggestive of common atrioventricular canal. These abnormalities of the QRS have been described as indicative of right bundle branch block with left axis deviation.[28] The iso-electric plane of T between V_1 and V_2 indicates slight forward orientation of the mean axis. Hemodynamics: normal pressure in the right side of the heart (pulmonary arterial pressure = 32/12); pulmonary blood flow = 12 l/min/m^2. Surgical findings: low atrial septal defect; normal mitral and tricuspid valves.

case can be determined. In the determination of the mean electric axis of the P or T wave in the "horizontal" plane (V leads), the assumption is made that the electric center[20,25,26] and the classic precordial leads all lie in the same "horizontal" plane, with V_2 perpendicular to the frontal plane. The mean axis of P may be directed anterior, posterior, or parallel to the midaxillary line. These data are more conveniently reported in terms of the point of intersection of the iso-electric plane[27] (which is perpendicular to the mean axis of P) with the precordium. When the mean electric axis is directed to the left, the sum of the electric forces of P in any lead recorded at the precordial surface to the right of the iso-electric plane will be negative and that in any lead recorded to the left of this plane will be positive. Thus, it is possible to identify the point of intersection with precision. The presence of wholly or predominantly positive P waves (Fig. 4–6) in tracings recorded from leads to the right of V_2 indicates that the direction of the mean axis lies anterior to the midaxillary line, whereas wholly or predominantly negative P waves recorded to the left of V_2 indicate that the mean axis of P is directed posterior to the midaxillary line. The distribution of the iso-electric plane and the mean electric axis of P in the "horizontal" plane for each case can be readily deduced from Table II. The configuration of P for each precordial lead can be deduced, knowing that the loop in the "horizontal" plane rotates counterclockwise.

TABLE II

Configuration of P and T Waves in Six Precordial Leads

Lead	Phase of P Waves* (90 patients)			Phase of T Waves* (83 patients)		
	+	+−	−	+	−+	−
V_1	27	40	23	3	15	65
V_2	78	10	2	55	1	27
V_3	88	2	0	64	5	14
V_4	90	0	0	69	4	10
V_5	90	0	0	73	6	4
V_6	90	0	0	79	4	0

* Symbols show phases as follows: + is positive; +− is initially positive and finally negative; −+ is initially negative and finally positive; − is negative.

In six patients, the alteration of the P wave was considered indicative of enlargement of the left atrium (Fig. 2), while the changes in another six patients were suggestive, but not indicative, of such enlargement (Fig. 1). In 36 patients, the alterations of the P wave (Fig. 5) or the QRS complex in V_1 (Fig. 7–9) or both were considered indicative of enlargement of the

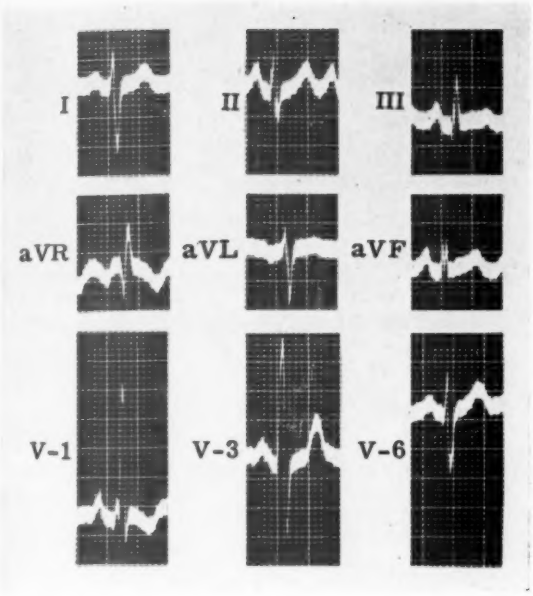

Fig. 5. Tracings from a five-year-old girl obtained three days before hemodynamic studies. Note the striking Rs in V_1 with slurring in the ascending limb as seen in instances of "systolic overloading" of the right ventricle. The P wave is suggestive of enlargement of the right atrium. Hemodynamics: pulmonary arterial pressure = 45/15; pulmonary blood flow = 10 l/min/m². Surgical findings: a defect in the middle of the atrial septum was found. A thrill was palpable over the base of the pulmonary artery, considered by the surgeon as indicative of insignificant pulmonary stenosis. The mitral and tricuspid valves were normal

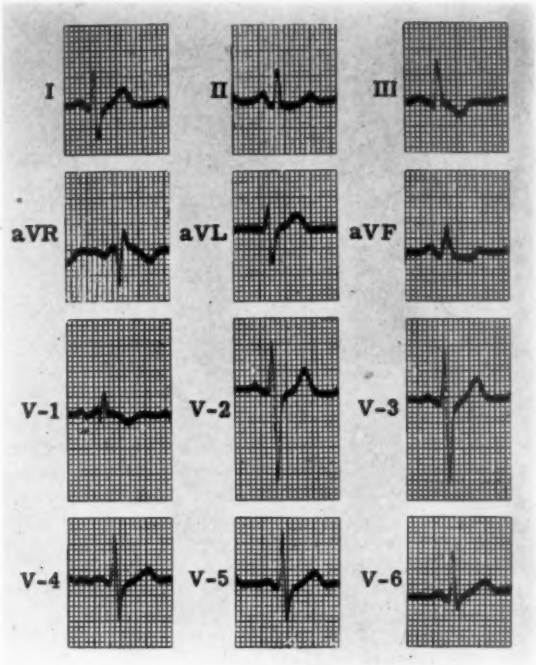

Fig. 6. Tracings from a 43-year-old woman obtained ten days before cardiac catheterization. The mean axis of P is directed forward, with the iso-electric plane to the right of V_1 (P positive from V_1 to V_6). The iso-electric plane of T is between V_1 and V_2. Hemodynamics: normal pressure in the right chambers of the heart (pulmonary arterial pressure = 32/16); pulmonary blood flow = 6.3 l/min/m². Surgical findings: sievelike defect of the atrial septum. Mitral insufficiency, grade 2, detected during operation.

right atrium, whereas the findings in 20 patients were suggestive but not indicative of such enlargement. In 25 patients, the P wave was considered to be within normal limits (Fig. 4, 8). In seven of the aforementioned nine patients with auricular fibrillation, an initial q wave, suggestive of enlargement of the right atrium,[29] was found in V_1.

QRS COMPLEX

Electric Axis: Figure 3 shows the distribution of the mean electric axis of the QRS complex over the frontal plane in 99 patients. In 97 patients, the axis of QRS was distributed within an angle of 120 degrees, that is, between +80 and −160 degrees. In one patient, the mean electric axis was at −30 degrees, whereas it was at −60 degrees in another; the process o ventricular activation in these two patients is similar to that previously described as indicative of the electrocardiographic abnormality seen in common atrioventricular canal.[1] It was impossible to determine the axis precisely in the remaining patient.

Duration: The duration of the QRS complex was measured in one of the standard leads (usually lead II). In 19 patients this duration exceeded 0.12 sec (Fig. 1, 2, and 9), with a maximum of 0.16 sec in one instance. The duration of the QRS complex was less than 0.12 sec in the remaining 81 patients, the shortest value being 0.07 sec in three patients. The average QRS duration by decades is given in Table I.

Configuration: Vectorial analysis of the QRS complex in the frontal plane showed that the vectors representative of the forces of the final part of ventricular activation were directed to the right in all cases. An S wave, usually

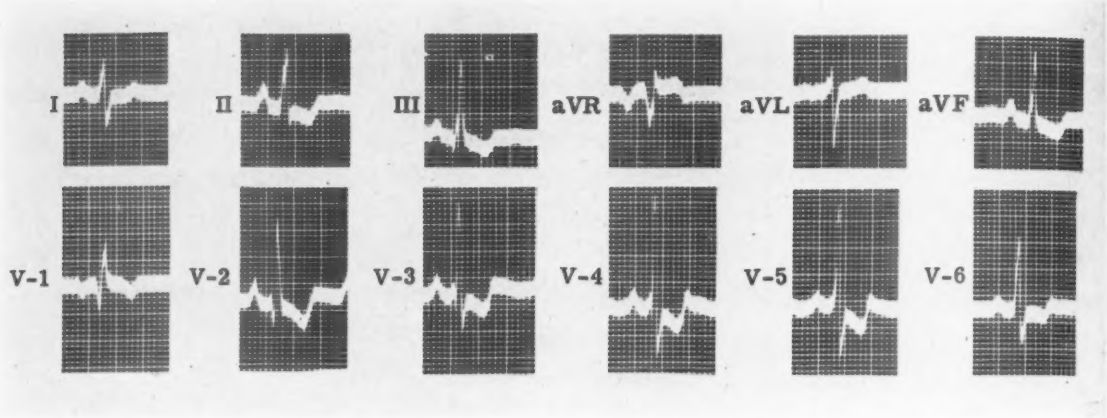

Fig. 7. Tracings from a 29-year-old woman obtained nine days before cardiac catheterization, showing depression of the ST segment and alteration of the T wave as in Figure 9. The iso-electric plane of T intercepting simultaneously V_3, V_4, V_5, and V_6, and also the mean electric axis being perpendicular to lead II in the frontal plane, indicate a mean axis directed behind the axillary line and upward. Abnormalities of the P and a QR in V_1 are indicative of enlargement of the right atrium. The mean axis of P is oriented in front, with the iso-electric plane intersecting V_1. Hemodynamics: normal pressure in the right side of the heart (pulmonary arterial pressure = 30/15); pulmonary blood flow = 21 l/min/m^2. Surgical findings: large atrial septal defect in the middle of the septum; normal mitral and tricuspid valves.

slurred, was a constant finding in lead I. The direction of this final vector varies, which results in a variety of configurations in the remaining standard or unipolar extremity leads. In one group of 16 patients, there was a final S wave in leads II and III (Fig. 8), indicating that the final vectors directed to the right are oriented above the axis of −150 degrees. In a second group of 54 patients, the final vectors lay between −150 and +150 degrees, indicated by the absence of a final S wave in lead III (Fig. 2, 4, 5, 7, and 9). In a third group of 23 patients, the final vectors were below +150 degrees, as indicated by the absence of S waves in leads II and III (Fig. 1 and 6).

In contrast, the initial vectors of ventricular activity were distributed more widely. In two patients, the initial vectors were directed to the right and above the line of −150 degrees, as indicated by a q wave found in the three standard leads (qRs or qrS in lead I; qR with or without a final s in leads II and III). In 11 patients, the initial vectors were directed below the axis of +150 degrees, causing an initial q in lead I but an initial positive deflection in leads II and III (Fig. 8) (QS in three patients and qrS or qRS in eight patients in lead I; R with or without s in lead II; R or rsR′ with or without s′ in lead III). In 23 patients, the initial vectors of ventricular activation were directed to the left and above the axis of −30 degrees (Fig. 2), with an initial positive deflection in lead I and a negative deflection in leads II and III (rS or RS in lead I; qR in leads II and III, with or without s in lead II or leads II and III). In 33 patients, the initial vectors were found between −30 and +30 degrees, with an initial positive deflection in leads I and II and a q in lead III (Fig. 5 and 7) (rS or RS in lead I; R with or without s or S in lead II; qR with or without s in lead III). In the remaining 24 patients, the initial vectors were directed below the axis of +30 degrees, with an initial positive deflection in the three standard leads (Fig. 6 and 9) (rS or RS in lead I; R with or without s in lead II; rsR in 11 patients, RR [or rR] in four patients and R in nine patients in lead III).

In 92 of the 93 patients just mentioned, the loop representing the process of ventricular action over the frontal plane rotated in a clockwise direction. In one other patient, the perpendicular projection of the loop over the frontal plane did not permit the determination of the rotation of the loop over this plane. In the remaining seven patients, the loop of ventricular activation over the frontal plane was similar to that already described in common atrioventricular canal, corresponding to types

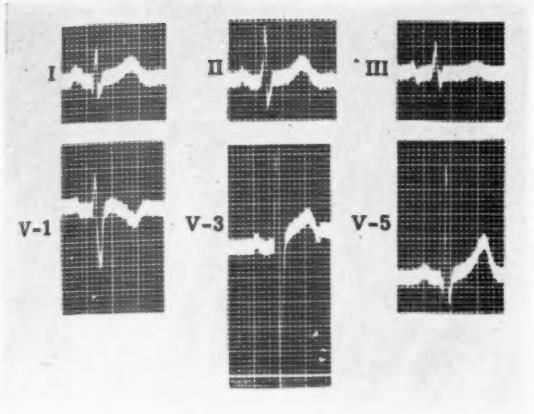

Fig. 8. Tracings from a 19-year-old boy obtained three days before cardiac catheterization. This was one of four patients with normal electrocardiograms and the only one in whom the direction of rotation of the QRS loop in the frontal plane was not determined. Hemodynamics: normal pressure in the right side of the heart; pulmonary blood flow = 5.6 *l*/min/m². Surgical findings: small atrial septal defect; normal mitral and tricuspid valves.

3 and 4 of Silverblatt and associates.[30] In one of these seven patients, the loop rotated in a counterclockwise direction above the zero point (Fig. 4), whereas the loop in the remaining six patients could be represented by a horizontally disposed figure "8" (qRS to qRs in three patients and RS in four patients in lead I; rS in five patients and rSr′s′ in two patients in lead II; rSr′ in all instances in lead III, with an additional s′ in one patient). The configuration in the last seven patients corresponded to that described as indicative of right bundle branch block associated with left axis deviation.[28]

The configuration of QRS in any unipolar precordial lead for any of the described group can be deduced easily. Table III is based on the frequency of the different configurations of the QRS complex in V_1.* Twelve patients showed no evidence for diastolic overloading (Fig. 5 and 8) in the right ventricle[7] (four patients had rS, one had QS, two had RS or R, and five had RS or R in V_1 and all had a QRS duration less than 0.12 second); in four of these, both the configuration and the time of the intrinsicoid deflections were normal (Fig. 8). A total of 88 patients showed either abnormal-

* See explanatory footnote in Table III.

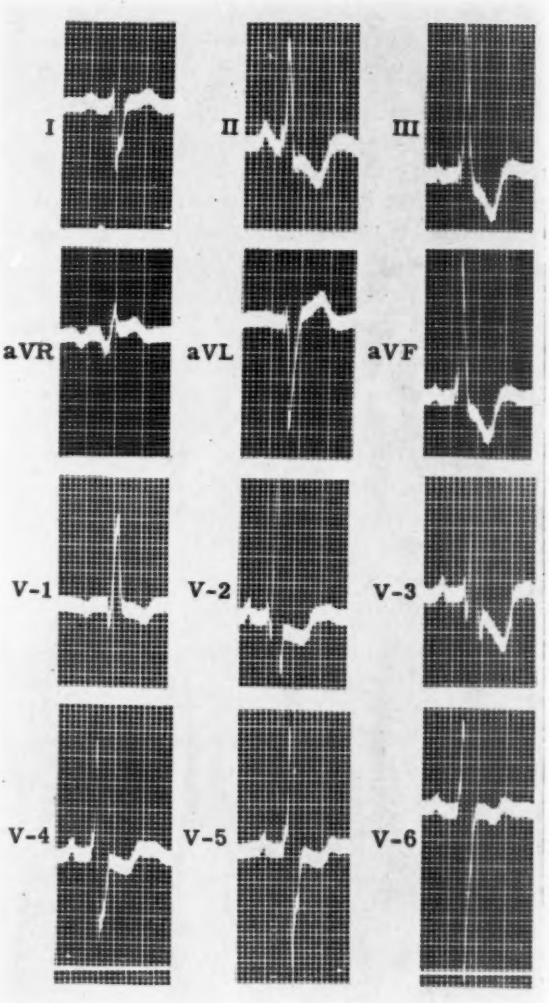

Fig. 9. Tracings from a 37-year-old woman obtained one day before the hemodynamic study. The QRS complex in V_1, indicating diastolic overloading of the right ventricle associated with a transitional type of configuration (RS) through V_6, was noted in 63 cases. Alterations of the ST segment and T wave are similar to those in isolated overloading of the right ventricle (seen also in Fig. 1, 2, and 7). The iso-electric plane of the T wave intersecting V_6, with T wave negativity in leads II and III, indicates backward and upward orientation of the mean axis. The iso-electric plane of the P wave lies between V_1 and V_2. Hemodynamics: increased pulmonary arterial pressure (75/26); pulmonary blood flow = 4.5 *l*/min/m². Surgical findings: large defect in the middle of the atrial septum; no other abnormalities described during operation.

ities in configuration or some delay of the intrinsicoid deflections in V_1 (Fig. 1, 2, 4, 6, 7, and 9). Lead V_1 in all these patients showed a configuration of the type considered to be

TABLE III

QRS Complex in V_1 and V_6 Related to Incidence of Normal R/S Ratios, Intrinsicoid Deflections and Pulmonary Arterial Pressure and Blood Flow Index in 100 Cases of Atrial Septal Defect

Lead V_1					Lead V_6 configuration		Mean pulmonary arterial pressure, mm Hg			Pulmonary index, L/min/m²		
Configuration	Duration QRS, seconds		R/S <1	Intrinsicoid deflection <0.03 second								
	>0.12	<0.12			RS	QRS	<25	25–40	>40	<5	5–10	>10
RsR to rSR	13	32	4	1	28	17	23	17	5	1	9	30
qR to QR	5	21	0	0	23	3	7	12	7	0	4	22
qRs	0	4	0	0	4	0	1	1	2	2	0	2
RSRS to rSRs	1	12	0	0	8	5	4	8	1	0	5	7
rS	0	4	4	4	0	4	2	2	0	0	2	2
QS	0	1	1	1*	0	1	1	0	0	0	1	0
RS to R	0	2	0	0	1	1	0	1	1	0	0	2
"RS" to "R"†	0	5	0	0	1	4	1	3	1	0	1	3

* Measurement of intrinsicoid deflection not done because of the QS configuration.

† Complexes with slurred and notched components, considered by Barker and Valencia[31] and by Sodi-Pallares and associates[22] as an "intermediate" type of right bundle branch block.

TABLE IV

Configurations in Leads I and V_6 Correlated with Overloading of Left Ventricle

		Configuration in V_6			
		RS (65 patients)		QRS (35 patients)	
		With overloading	Without overloading	With overloading	Without overloading
Configuration in lead I	QS	1	1	2	0
	QRS	0	1	2	7
	RS	8	54	10	14

indicative of diastolic overload of the right ventricle.[10]

Thirty patients had an initial q wave in V_1 (Fig. 7 and 9); four of these had a final s wave. A majority of the tracings (74) were without a final s wave in V_1.

In V_6, two types of configuration were found. In 65 patients, the complex was RS (variation of rS to Rs) (Fig. 1, 4, 6, 7, and 9). The remaining 35 patients had initial q waves (qrS to qRs) (Fig. 2, 5, and 8). Ten of the 12 patients without the diastolic-overloading type of complex in V_1 had a qRS in V_6 (Fig. 8). The frequency of various configurations in lead I associated with these types is given in Table IV. The presence of q in lead I was almost always associated with q in V_6.

T WAVE

The mean electric axis of the T wave in the frontal plane calculated from the three standard leads was determined in 90 patients. This evaluation was not possible in the remaining patients because of the effect of digitalis and auricular fibrillation on the ST segment and the T wave. In 74 of the 90 patients, the T wave lay in an angle of 90 degrees, ranging from −20 to +70 degrees (Fig. 4, 5, 6, and 8). In 21

instances, the mean axis of T lay in or above the axis ±0 (Fig. 1, 2, 7, and 9); in three of these, the changes were considered to result from primary alteration of repolarization. The mean electric axis was not directed to the right in any instance.

In the "horizontal plane," the mean axis of T is more conveniently described in terms of the intersection of the iso-electric plane with the precordium, as was done for the P wave. This was determined in 83 patients (Table II); in the remaining 17 patients, auricular fibrillation, the effect of digitalis or an absence of leads did not permit precise determination of the mean axis of T. Since the direction of rotation of the loop representative of the T wave is opposite to that representing the P wave, identical positions of these mean vectors (and hence of the iso-electric plane representative thereof) are represented by waves of reversed phase. Isolated negative T waves were found in two tracings among the 69 in V_4 and the 73 in V_5 considered to be in the zone of positivity. In eight tracings among those in V_2, V_3, and V_4 (Fig. 1) or V_4, V_5, and V_6 (Fig. 2 and 7) considered to be in the zone of positivity, a diphasic transitional wave initially negative and finally positive was consistently found. Such findings result from the fact that all the precordial leads are not exactly in the same plane. In 55 patients, the mean electric axis of the T wave was directed anterior to the midaxillary line (Fig. 4 and 6), whereas the mean axis was directed posterior to this position in 26 patients (Fig. 7 and 9). The position of the axis and the configuration of the T wave were considered as normal (Fig. 4, 5, and 8) or as secondary (Fig. 1, 2, 7, and 9) to overloading of the right ventricle or digitalis effect or both in all but three patients, in whom the changes were considered as secondary to myocardial ischemia.

INTRINSICOID DEFLECTION

The value of measurement of the "intrinsicoid deflection" in lead aVR is limited because of the difficulty of precise determination of the end of this interval. Of 84 patients, three did not show intrinsicoid deflections (QS), whereas in six this measurement was 0.06 sec or less (Fig. 5) and in 19 others problems of measurement permitted only the estimate of durations between 0.06 and 0.08 sec (Fig. 6 and 7). In the remaining patients, this interval exceeded 0.08 sec (Fig. 9), although precise measurement could not be made in many instances (Fig. 1, 2, and 4). In lead V_1, the intrinsicoid deflection was measured in 80 patients (19 others had complete right bundle branch block and the remaining one had a QS); only five of these 80 had measurements less than 0.03 sec. Thus, the intrinsicoid deflection was in excess of 0.03 sec in the remaining 75 patients plus the 19 who had complete right bundle branch block, giving a total of 94. In V_6, the intrinsicoid deflection was delayed in 15 of 35 patients (those showing q waves), with a maximal value of 0.055 sec (one patient).

INDEXES

Several indexes considered by various authors[33–36] to indicate ventricular overloading were studied.

Index of Lewis: $(R_1+S_3)-(R_3+S_1)$: In 27 instances, this index was less than −14, suggesting overload of the right ventricle. Pulmonary hypertension with pressures greater than 60 mm of mercury was detected in 13 of the 17 patients who had indexes less than −17. In 60 patients, the indexes varied from −14 to 0, while they ranged from +1 to +7 in the remaining 13 patients.

Q/R or S/R in aVR: Of 84 electrocardiograms measured, only 23 showed a value for this ratio of 1 or less. The R was larger than 5 mm in 25 instances.

R/S in V_1: Only nine patients had a R/S index in V_1 less than 1, and the intrinsicoid deflection in five of these was less than 0.03 second (Table III). The index was abnormal, varying from 7 to 22, in all patients who had complete right bundle branch block. The R was larger than 7 mm in 53 patients; it was larger than 20 mm in only three patients, the maximum being 24 mm. The s wave measured 2 mm in 10 patients and less than 2 mm in 30.

R/S in V_6: In 26 patients, this ratio was less than 1; it varied from 1 to 14 in the remaining instances. The R was less than 4 mm in only 10 patients, whereas it was 21 mm or more in

nine. The S was deeper than 7 mm in 48 instances.

R in V_6 + S in V_1: This value was greater than 35 mm in five instances.

R in V_1 + S in V_6: This value was greater than 10.5 mm in 71 patients.

R/S in V_6: R/S in V_1: This index was less than 0.4 in 30 patients. The values in the remaining instances varied from 0.6 to 14.

When the denominator was less than 0.1 millivolt in any of these ratios, the value for the numerator was recorded as the index. Of these various indexes, only the R/S ratio in V_1 and the value for R in V_1 plus S in V_6 were abnormal in the great majority of cases (91 and 71 per cent, respectively). The other indexes did not permit useful conclusions to be made. Some overloading of the right ventricle was the principal or, in the great majority of patients, the only functional abnormality. The values of these measurements as indexes of cardiac function must be questioned.

Hemodynamic Studies

The right ventricular systolic pressure exceeded 40 mm of mercury in 47 patients, in six of whom it was more than 90 mm (Table V). The pulmonary blood flow in 93 patients is summarized in Table III. The pulmonary index was less than 5 *l*/min per square meter of body surface in only three of these patients, all of whom had pulmonary hypertension. Of the 18 patients with complete right bundle branch block in whom the pulmonary blood flow was determined, 10 had flows in excess of 10 *l* (Fig. 2). A left to right shunt was present in all but one of the patients on whom studies for shunts were made. The total pulmonary resistance was calculated in 93 patients, in 75 of whom it was found to be within or below the range of normal. In five of the remaining 19 patients, the total pulmonary resistance exceeded 600 dynes sec cm^{-5}. Systemic arterial hypertension was confirmed in four patients during hemodynamic studies.

TABLE V

Right Ventricular Systolic Pressure in 100 Cases of Atrial Septal Defect

Systolic pressure in right ventricle, mm Hg	Patients
40 or less	53
41–60	25
61–90	16
91–130	6

Surgical and Necropsy Findings

A total of 17 patients had associated anomalous connection of the pulmonary veins to the right atrium or to a tributary of this chamber. The condition of the atrioventricular valves and the presence or absence of valvular insufficiency were reported by the surgeon in 89 of the 100 patients. Definite mitral insufficiency was present in 11 patients, and mitral insufficiency was not excluded with certainty in two others. Sixteen patients showed evidence of tricuspid insufficiency at operation. In one instance, a systolic thrill felt by the surgeon was considered indicative of aortic valvular disease. Pericarditis was diagnosed at the time of operation in three patients; it was of the constrictive type in one instance. A patent ductus arteriosus was present in one patient in addition to the atrial septal defect.

The relation of the electrocardiographic findings in lead V_6 to the presence of additional malformations or functional conditions of the left ventricle is shown in Table VI. In 35 patients, the presence of q in V_6 made possible the measurement of the intrinsicoid deflection

TABLE VI

Correlation of Lead V_6 with Evidence of Overloading of Left Ventricle

Evidence of overloading of left ventricle	Configuration in V_6	
	RS (65 patients)	QRS (35 patients)*
Surgical findings	8	6
Clinical and catheterization data	1	8

* Sixteen of these 35 patients gave electrocardiographic evidence of overloading. Subsequent surgical and clinical data failed to confirm this in four of these 16 patients.

(Fig. 2, 5, and 8); in 14 of these patients, there was evidence, either from the surgeon's report or on a clinical basis, for overloading of the left ventricle. The duration of the intrinsicoid deflection in V_6 indicated the presence of left ventricular overload in 12 of these patients. Among the 65 patients with RS in V_6, nine presented surgical or hemodynamic evidence for left ventricular overload. Measurement of the duration of the intrinsicoid deflection in V_6 in this group of 65 patients was not done, and other electrocardiographic data to indicate overloading of the left ventricle were not found.

Relation of Hemodynamic Data to Electrocardiographic Findings

The principal functional derangement in atrial septal defect is an increase in pulmonary blood flow, sometimes complicated by an increase in pulmonary arterial pressure. An attempt was made to see whether the electrocardiographic pattern reflected these alterations. No specific configuration of QRS in V_1 was associated with a particular degree of increased pulmonary blood flow. The basic pattern RSR is common in patients who have mean pulmonary arterial pressures less than 20 mm of mercury, whereas the majority of patients with a Q or a RSRS pattern show mean pulmonary arterial pressures greater than this value. As already indicated, apart from the ratio R/S in V_1 and the value for R in V_1 plus S in V_6, the various indexes tested were of little value in differentiating the normal from the abnormal electrocardiogram. It was not surprising, therefore, that no correlation could be established between any of these indexes and the pulmonary arterial pressure, the pulmonary blood flow, the pulmonary resistance or the ratio of pulmonary arterial systolic pressure to systemic arterial systolic pressure. Of the 52 patients in whom the R/S ratios in V_1 were 3.0 or less, only two had values for pulmonary resistance in excess of 300 dynes sec cm^{-5}. Of 40 patients with R/S ratios in V_1 greater than 3.0, a total of 17 had pulmonary resistance in excess of 300 dynes sec cm^{-5}.

Comment

The present study, although restricted to patients in whom the severity of the illness necessitated surgical correction, probably is generally representative of results in patients with atrial septal defect. The patients studied encompassed both the very young and the the older age groups. Auricular fibrillation was relatively common, occurring in nine of these 100 patients; this contrasts to the finding of only one example of this arrhythmia in a review of the electrocardiograms in 100 proved cases of ventricular septal defect, none in 50 cases of the tetralogy of Fallot, one in 29 cases of common atrioventricular canal, one in 150 cases of patent ductus arteriosus, and one in 14 cases of complete transposition of the great vessels. In contrast to the experience of Bedford and associates,[37] we found no relationship between this arrhythmia and mitral disease.

Right Ventricular Overloading: If one assumes that the complex "RSR" does not represent right bundle branch block,[30,36,38–41] use of the measurement of the intrinsicoid deflection in V_1 as a principal indication of overloading of the right ventricle appears rational because of the precise definition of its upper limit of normal (0.03 sec in V_1). Evidence for abnormality of the dynamics of the right ventricle is demonstrated equally well by the ratio R/S in V_1 being greater than 1.0 in 91 of our 100 patients and the duration of the intrinsicoid deflection in V_1 in excess of 0.03 sec in 94 patients. These data would not appear to justify the opinion of Milnor and Bertrand[41] that the intrinsicoid deflection gives no diagnostic information in practice that is not provided by measurement of the total duration of the QRS. In only 12 of the 100 patients did the electrocardiograms fail to show some evidence of diastolic overload of the right ventricle. All these patients gave hemodynamic evidence of increased pulmonary flow, while three had moderately increased pulmonary arterial pressure.

Left Ventricular Overloading: The relatively high incidence of overloading of the left ventricle was unexpected. This aspect of the electrocardiogram of atrial septal defect has not been recognized heretofore. As already noted, a complete surgical report was available in 89 patients, including statements regarding the presence or absence of valvular deformity or

functional insufficiency. In a total of 23 patients, evidence based on either the surgical report (14 patients) or the available clinical or hemodynamic data (nine patients) indicated the presence of functional abnormality of the left ventricle (Table VI). Among the 65 patients with the RS configuration in V_6 were seven who had mitral insufficiency, grade 1 to 2, recognized by the surgeon, one with aortic valvular disease and one who had essential hypertension. For reasons already outlined, the diagnosis of the presence or absence of left ventricular overload on the basis of the intrinsicoid deflection in V_6 was not made in this group of patients. Among the 35 patients with the presence of q in V_6, a total of 14 presented data that could be interpreted to indicate abnormalities of the left ventricle. The principal evidence in six of these 14 patients was obtained at the time of operation; these included four patients with mitral insufficiency, one with patent ductus arteriosus and coarctation and one with aortic insufficiency. All six of these patients had electrocardiographic evidence of left ventricular overload in lead V_6. The other eight patients presented clinical data compatible with abnormal function of the left ventricle; electrocardiographic evidence of left ventricular overload was present in one of three patients with systemic arterial hypertension, in three patients thought to have mitral insufficiency (condition of valve not stated at the time of operation), in one patient with aortic insufficiency and in one with a history of toxemia of pregnancy on two occasions. In four other patients, the electrocardiogram was interpreted to indicate left ventricular overload, but supportive evidence for abnormality of left ventricular function was not found on either surgical or clinical grounds. However, two of these patients had constrictive pericarditis, and in another patient the status of the mitral valve at the time of operation was not recorded. Thus, a total of 16 of the 35 patients with the QRS configuration in lead V_6 gave electrocardiographic evidence of overloading of the left ventricle, which was substantiated with certainty in only 12 of these 16.

The presence of a q wave normally found in the left precordial leads occurred in only 35 per cent of these 100 patients with atrial septal defect. The configuration RS that occurred in the remaining 65 per cent could be explained by shifts of the transitional zone caused by clockwise and backward rotation[42] of the heart consequent to overloading of the right ventricle. The presence of a q wave in V_6 suggests that this transitional zone had not been so displaced in certain instances. This could result from associated overloading of the left ventricle, from external causes that present dextrorotation or, to a degree, from right ventricular overload insufficient to displace the transitional zone to the left precordial leads. From a practical standpoint, it would appear logical to seek an additional anatomic anomaly in a patient with atrial septal defect who exhibits a q wave in lead V_6.

Differentiation from Atrioventricular Canal: As mentioned earlier, conditions that may closely resemble atrial septal defect on a functional and clinical basis include common atrioventricular canal and total anomalous pulmonary venous drainage. All 30 of the patients who had an initial q wave in V_1 had severe hemodynamic alterations. Nevertheless, the relative frequency of this finding in such a group of patients limits its value as indicative of total anomalous pulmonary venous drainage, as suggested by Keith and co-workers.[43] With regard to the importance of differentiation of patients with common atrioventricular canal from those with atrial septal defect, it will be recalled that 93 of this group of 100 patients had a QRS axis lying within $+80$ to -160 degrees, and all but one of these 93 had a clockwise direction of rotation of the loop of ventricular activation in the frontal plane. Two patterns in the activation represented by the QRS loop have been described as typical of common atrioventricular canal.[1] The first is characterized by counterclockwise rotation of the loop of ventricular activation above the zero point, with the mean axis of QRS between -60 and -170 degrees; the other is manifested by a figure-of-eight configuration approximately paralleling the horizontal line ± 0 to ± 180 degrees. The QRS loop was similar to the latter appearance in six cases of atrial septal defect, whereas it was similar to the former in one instance. In two of these seven patients, a muscular rim completely sur-

rounded the defect; the defect in the remaining five patients was situated low in the atrial septum, lying just above the valvular ring, but a cleft of the mitral valve was not present.[3] Thus, the possibility of atrioventricular canal could be ruled out with certainty on the basis of the electrocardiogram in 93 cases, while this certain differentiation could not be made in the remaining seven.

The relative frequency of mitral insufficiency in association with atrial septal defect does not permit the diagnosis of common atrioventricular canal to be made based on the presence of mitral insufficiency, as suggested by Blount and associates[44] and by Milnor and Bertrand.[41] The abnormality of ventricular activation seen in common atrioventricular canal is not solely the result of insufficiency of the mitral valve. If the 29 proved cases of common atrioventricular canal studied at our institution are added to the present group, a 27 per cent incidence of the atypical group of activation is obtained. This is not too different from the incidence of 36 per cent of types 3 and 4 of Silverblatt and coworkers,[30] whose study was carried out on patients in whom the anatomic diagnosis was not established with certainty.

Summary and Conclusions

Electrocardiograms have been analyzed and correlated with hemodynamic data in 100 cases of atrial septal defect proved at operation at the Mayo Clinic. Included in this series were cases with anomalous connection of the right pulmonary veins, whereas cases of common atrioventricular canal and of total anomalous pulmonary venous drainage were excluded.

The loop of ventricular activation in the frontal plane was located below the zero point and had a clockwise rotation in 92 patients. In seven patients, the direction of rotation of the loop of QRS was counterclockwise and above the zero point, as has been uniformly found in cases of abnormalities of the atrioventricular canal.

Alterations of the P wave indicative of or suggesting enlargement of the right atrium were present in 56 patients.

Overloading of the right ventricle as indicated by delay in the intrinsicoid deflection or increased R/S ratio in lead V_1 was present in 94 patients, 88 of whom showed electrocardiographic evidence for diastolic overloading. The presence of diastolic overloading of the right ventricle was associated with a left to right shunt. No precise quantitative correlation could be established between the hemodynamic data and the electrocardiographic findings.

A q wave was present in lead V_6 in 35 patients, of whom 16 had electrocardiographic evidence for overloading of the left ventricle. Subsequent clinical or surgical data did not reveal a cause for the apparent "overloading" in four of these 16 patients.

Attention is drawn to the frequency of abnormality of the left ventricle in atrial septal defect, and to the differential diagnostic value of the loop of ventricular activation in the frontal plane.

Accurate anatomic appraisal is necessary for the precise categorization of the electrocardiographic patterns characterizing different forms of congenital heart disease, the complexities of which are frequently unrecognizable by currently available diagnostic methods.

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Phonocardiography in Atrial Septal Defect

External and Intracardiac Phonocardiograms*

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EXTERNAL phonocardiograms in atrial septal defect have been studied by Reinhold and Nadas,[1] Leatham and Gray,[2] Effert *et al.*,[3] and Soulié *et al.*[4] A systolic murmur and split 2nd sound over the 2nd left interspace were usually found. A delayed, short early diastolic murmur and a presystolic murmur or 4th sound were often recorded over several areas of the precordium. The presence of a presystolic murmur and a loud 1st sound at the apex may simulate the snapping 1st sound of mitral stenosis. The mechanisms of production of systolic and diastolic murmurs and abnormal heart sounds were tentatively explained.

Intracardiac phonocardiograms in atrial septal defect have not been studied systematically, although the method has been introduced by several workers.[5–9] The site of murmur formation may be precisely located in various cardiac chambers or great vessels (pulmonary artery) by intracardiac phonocardiograms. This comparative study, of external and intracardiac phonocardiography, correlated with intracardiac and vascular pressure tracings, may demonstrate, not only the site of murmur formation, but also the type of transmission of the murmur from the cardiac chambers to the precordium, and also explain the splitting of heart sounds.

Intracardiac phonocardiograms in one case of septal defect were presented by Luisada and Testelli[10] and other tracings were discussed by Luisada and Liu in a recent monograph.[11]

MATERIAL AND METHOD

External phonocardiograms were recorded in 16 patients and intracardiac phonocardiograms were also registered in 6 of the 16 cases.

The diagnosis was based on the data of right heart catheterization in all cases and on surgery in four of them. One patient (case 1) had simultaneous right and left heart catheterization. All patients, except two, had a left-to-right shunt (cases 1 and 14).

External phonocardiograms were recorded over the apex, at the 2nd, 3rd, and 4th (or 5th) left interspace, and at the 2nd, 3rd, and 4th right interspace. The same amplification was selected for all these areas and the stethoscopic method of the Sanborn Twin Beam was used. External phonocardiograms were also recorded over the same areas by the use of a low and high pass filter (Krohn-Hite) according to the method of "selective phonocardiography."[12]

Intracardiac phonocardiograms were recorded by the method of Luisada and Liu.[8] In this, the low frequency vibrations initiated from the strain gauge (P 23 D) are filtered out while the medium and high frequency vibrations are amplified and filtered through a built-in system of filters. Intracardiac phono was recorded by a cathode-ray photographic device with simultaneous pressure tracing and electrocardiogram.

RESULTS

EXTERNAL PHONOCARDIOGRAMS

The findings are tabulated in Table I and illustrated in Figures 1 and 2.

The 1st sound was split over several areas in 7 of the 16 patients; at the apex, in 6 instances; at the 4th left interspace, in 3; over the 2nd and

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TABLE I

Findings in External Phonocardiograms in 16 Cases of Atrial Septal Defect

Name, sex, and age	Intensity of systolic murmur						Splitting of sounds		4th sound	Diastolic murmur	Pulmonary artery	Pulmonary blood flow
		Left sternal border			Right sternal border							
	Apex	2nd	3rd	4th	2nd	4th	1st sound	2nd sound			pressure	*l/m*
1. L. E. F 36	+	+	+	+	+	−	Prolonged	Prolonged	Apex, 4th, LSB	−	107/55	2
2. L. J. M 16	+	Diam. +++	++	++	+	+	Apex, 3rd, 4th, LSB	All over	Apex, 2nd, LSB	−	30/10	12
3. M. N. F 42	++	++++	+++	+++	++	++	−	All over	Apex, 2nd, 3rd, LSB	−	34/7	8.8
4. F. B. F 14	+	Diam. ++	+	+	Diam. ++	+	−	All over	−	−	24/7	4
5. C. G. F 19	+++	++	++	+	+	+	Apex, 2nd, 3rd, LSB	4th, LSB	Apex, 3rd, 4th, LSB	−	80/42	5
6. B. L. F 4	+	++	−	−	+	+	2nd, 3rd, LSB	2nd, LSB	−	Apex Mid-d.	22/8	—
7. S. M. M 9	+++	++	−	++	+	+	−	2nd, LSB, 4th, RSB	Apex, 3rd, 2nd, 4th, LSB	−	27/12	3
8. H. J. M 4	+	++	+	+	+	+	−	−	−	−	42/7	11
9. O. H. M 28	+	+++	0	++	+	++	Apex, 4th, 2nd, LSB	Apex, 2nd, LSB	2nd, LSB	Early, 2nd, 3rd, LSB, 4th, RSB	25/14	24
10. T. C. F 27	+	+++	++	++	+	+	−	Apex, 2nd, LSB, 2nd, RSB	−	Early d. 2nd, 3rd, 4th, LSB	32/16	15
11. W. J. F 6	+	++	++	+	+	++	−	−	2nd, 3rd, 4th, LSB	−	42/18	4
12. I. Z. F 9	++	Diam. ++++	0	+++	+++	++	−	2nd, LSB	−	−	20/7	5
13. F. R. M 13	++	Diam. +++	Diam. ++	++	Diam. ++	+	−	−	−	−	12/7	2.3
14. N. M. F 17	+	++	0	+	−	−	−	2nd, 4th, LSB	−	−	116/66	—
15. C. C. F 16	−	+	0	+	+	+	Apex, 2nd, L RSB	−	−	Early d., Apex, 2nd, 4th, LSB	19/7	4.6
16. B. C. M 59	+	+	0	+	+	−	Apex, 2nd, L RSB	2nd, LSB	−	Early d., Apex, 2nd, 4th, LSB, 4th, RSB	38/3	10

Diam. = diamond-shaped systolic murmur. Mid-d. = mid-diastolic vibrations. Early-d. = early diastolic murmur. L-RSB = left-right sternal border.

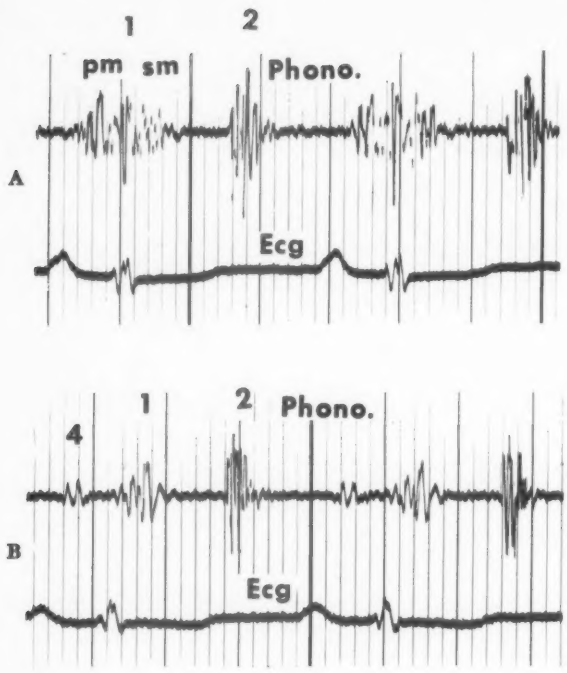

Fig. 1. Case 1. Phonocardiogram, stethoscopic tracing: (A) at apex (presystolic and systolic murmurs) = split and prolonged 1st sound followed by systolic murmur; (B) over pulmonic area (4th sound, systolic murmur, and prolonged 2nd sound).

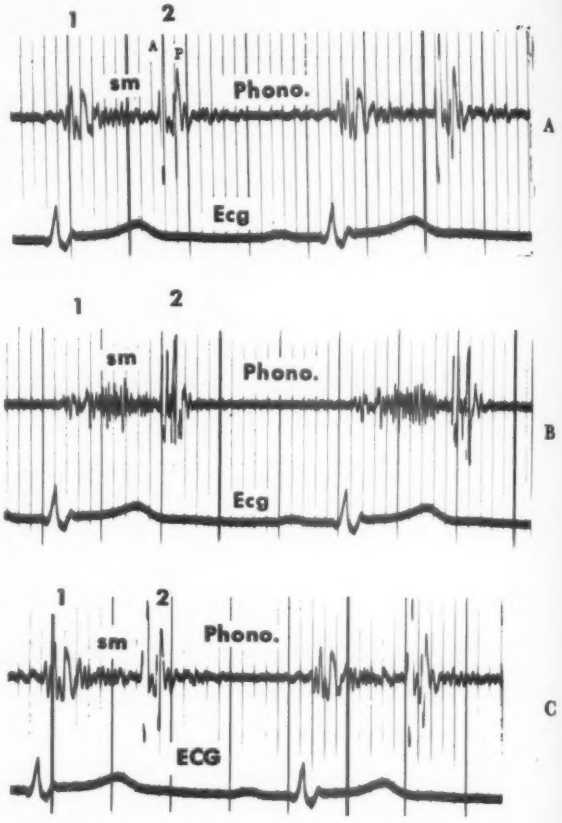

Fig. 2. Case 2. Phonocardiogram, stethoscopic tracing: (A) at apex (split 1st sound, systolic murmur, split 2nd sound); (B) over pulmonic area (split 1st sound, diamond-shaped systolic murmur, split 2nd sound); (C) recorded at 4th left interspace (systolic murmur in decrescendo). A = aortic component and P = pulmonic component of 2nd sound.

3rd interspaces in 4; and over the 2nd right interspace, in 2. The intensity of the 1st sound was greater at the apex, mid-precordium, and left lower sternal spaces. The 1st sound, however, was not definitely prolonged, except in case 1.

A systolic murmur was recorded in all the 16 patients at the 2nd left interspace (Table I); in 9, also over the apex and 3rd left interspace; in 12, also over the 4th left interspace and 2nd right; and in 10, over the 4th right interspace. The maximum intensity of the systolic murmur was at the 2nd left interspace. The intensity of the systolic murmur over the left 4th and 5th interspaces was the same or greater than at the 3rd left interspace.

The 2nd sound was split at the 2nd left interspace in 11 of the 16 patients; it was prolonged without splitting in one. One patient who had pulmonary hypertension (case 5) had a split 2nd sound over the 4th left interspace only. However, over other areas the 2nd sound was only prolonged. The amplitude of the 2nd sound was unusually large. The last component of the second sound coincided with the closure of the pulmonic valve.

An early diastolic murmur was recorded at the 2nd right interspace in one patient, and over the 2nd and 3rd left interspaces in 4. In the latter it was also recorded either over the left or right 4th interspaces. Few mid-diastolic vibrations were recorded in one patient over the apex (case 6) (Fig. 3).

A 4th sound was best recorded at the apex in 5 patients; in 4 of them, a sound of small amplitude was also recorded over the left sternal border, but not over the right. In 4 patients, the 4th sound contained several vibrations, so that it could be termed as a presystolic murmur or atrial murmur (Fig. 1 A and B).

TABLE II
Intracardiac Phonocardiograms in 6 Cases With Left-to-Right Shunt

	Name	Age	Systolic murmur					Splitting of sounds		Diastolic murmur					Presystolic murmur		
			RV	PA	RA	LA	LV	1st sound	2nd sound	RV	PA	RA	LA	LV	PA	RV	LV
1	L. E.	36	−	−	+	++	++	Prolonged	−	−	+	++	++	+	+	+	+
2	L. J.	16	+	Diam. ++	+	+	−	PA, RA	−	++	−	+	−	−	+	−	+
3	M. N.	42	+	Decre. ++	−	0	0	RA	PA	−	−	−	0	0	+	+	−
4	F. B.	14	Diam. ++	+	+	+	0	−	RA	+	+	+	0	0	−	−	0
5	C. G.	19	+	++	+	0	0	−	PA	++	+	+	0	0	−	−	0
6	B. L.	4	+	Diam. ++	+	0	0	−	−	Early +	Early	−	0	0	−	−	0

RV = right ventricle; PA = pulmonary artery. RA = right atrium; LA = left atrium; LV = left ventricle.

In no instance was a *3rd sound* definitely identified in this series of cases.

INTRACARDIAC PHONOCARDIOGRAMS (TABLE II)

A systolic murmur was recorded in the pulmonary artery and right ventricle in all cases having a left-to-right shunt and in 4 of them, in the right atrium (Fig. 4–6). The amplitude of this murmur was greater in the pulmonary artery than in the right ventricle or atrium.

The 1st sound was split in two patients, in the right atrium and pulmonary artery. *The 2nd sound* was split in the pulmonary artery in 2 cases, and in the right atrium in one. *A 4th*

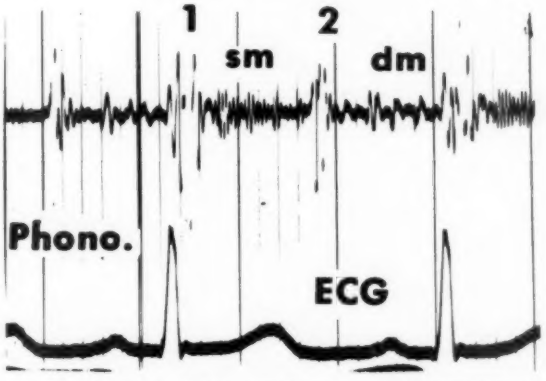

Fig. 3. Case 6. Phonocardiogram, stethoscopic tracing: recorded at apex (systolic murmur, mid-diastolic vibrations).

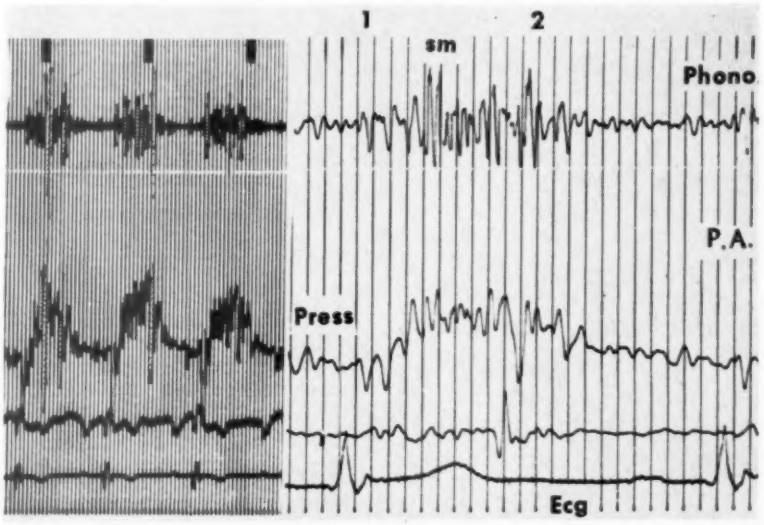

Fig. 4. Case 2. Pulmonary artery: intravascular phono (split 1st sound, systolic murmur). Film speeds 25 and 100 mm/sec. Time lines: 0.04 sec.

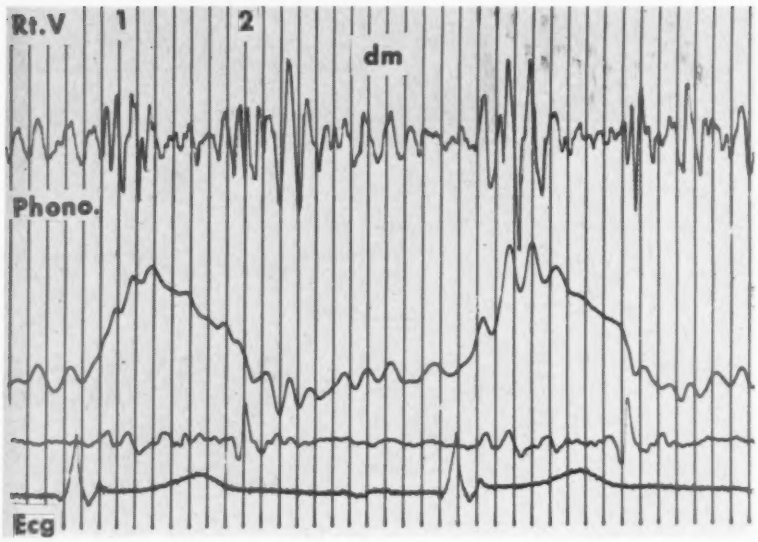

Fig. 5. Case 2. Right ventricle: intracardiac phono (faint systolic murmur, diastolic murmur).

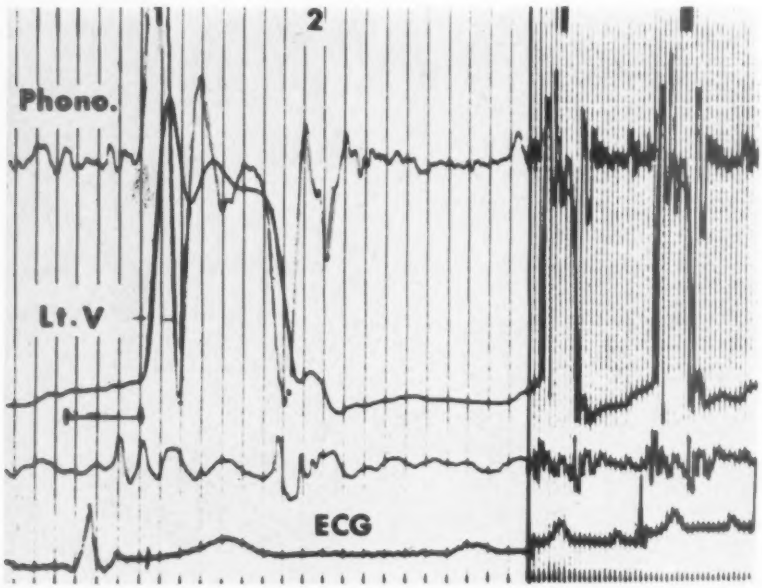

Fig. 6. Case 2. Left ventricle: intracardiac phono (no murmurs). Film speeds, 25 and 100 mm/sec. Time lines 0.04 sec.

heart sound (or a presystolic murmur) was recorded in the left ventricle, pulmonary artery and right ventricle in one case (case 1), in the left ventricle and pulmonary artery of another (case 2), and in the right ventricle and pulmonary artery of a third patient (case 3).

An early diastolic murmur was recorded in the pulmonary artery and right ventricle in one patient in whom only a few low frequency diastolic vibrations were recorded over the apex (case 6). A mid-diastolic murmur was recorded in the right ventricle, pulmonary artery, and right atrium of three cases, with the greatest intensity in the right ventricle (Fig. 4–6).

COMPARISON OF EXTRACARDIAC AND INTRACARDIAC PHONOCARDIOGRAMS

Left-to-Right Shunt: In comparing the extracardiac (Fig. 2 and 3) and intracardiac phonocardiograms (Fig. 4–8) in one of the 5 patients (case

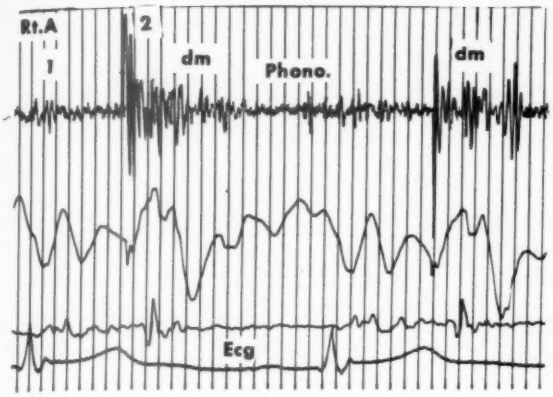

Fig. 7. Case 2. Right atrium: intracardiac phono (split 1st sound, faint systolic murmur, diastolic murmur). Film speed 100 mm/sec. Time lines: 0.04 sec.

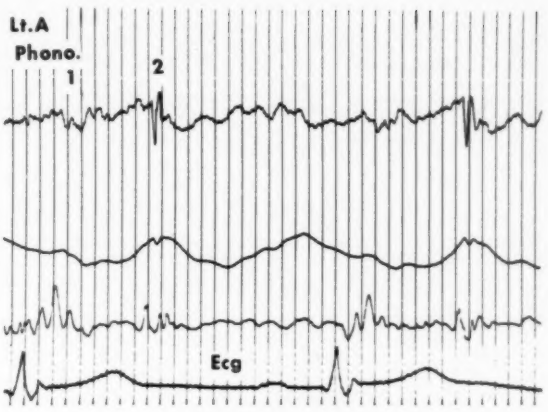

Fig. 8. Case 2. Left atrium: intracardiac phono (no murmurs). Film speed 100 mm/sec. Time lines 0.04 sec.

2) with a left-to-right shunt, the following observations were made. The 1st sound was widely split, especially over the apex and 3rd left interspace. The 1st component of the 1st sound within the right heart was 0.06 sec after the Q wave of the electrocardiogram and coincided with the closure of the tricuspid valve (Fig. 5). The 2nd component of the 1st sound within the pulmonary artery and right ventricle was 0.08 sec after the Q of ECG and coincided with the opening of the pulmonic valve. These two components of the 1st sound in the right heart coincided with the 1st half component of the 1st sound externally. The first component of the 1st sound within the left heart started 0.13 sec after the Q of ECG and coincided with the beginning of the left ventricular upstroke or closure of the mitral valve. The 2nd component of the 1st sound within the left heart started 0.16–0.17 sec after the Q of ECG and coincided with the opening of the aortic valve. Both components of the 1st sound in the left heart coincided with the 2nd component of the 1st sound of the external phonocardiogram (Table III).

Therefore, *splitting of the 1st sound in this case was due to a delayed closure of the mitral valve* and an unavoidable delayed opening of the aortic valve.

The systolic murmur had various shapes: at the 2nd left interspace (as well as within the pulmonary artery), it was diamond-shaped; over several other precordial areas (as well as within the right ventricle and atrium), it was in decrescendo.

The 2nd sound was split over the precordium and its 1st component coincided with the 2nd sound recorded in the left heart. The 2nd component (precordial) coincided with the 2nd sound recorded within the pulmonary artery, indicating a delayed closure of the pulmonic valve. A short diastolic murmur was recorded

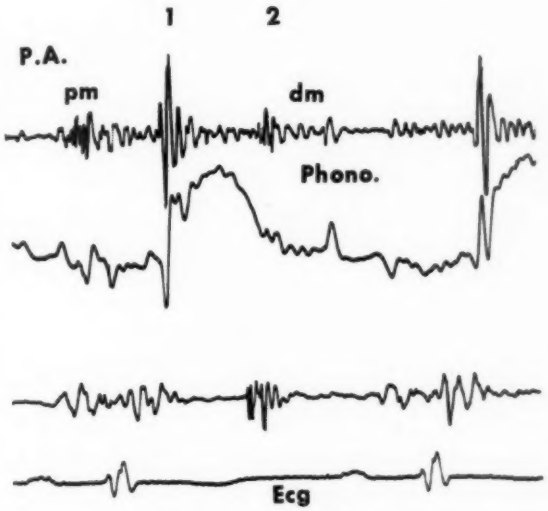

Fig. 9. Case 1. Pulmonary artery: intravascular phono (presystolic murmur, prolonged 1st sound, diastolic murmur). Film speed: 100 mm/sec.

within the right ventricle and atrium, but was not recorded over the precordium. A 4th sound was recorded over the apex; a similar murmur was well recorded within the left ventricle and pulmonary artery.

TABLE III
Comparison of Onset of Electrical and Mechanical Systole

	Name	Age	Sex	Distance in seconds between the Q of the ECG and systolic rise of intracardiac pressure curves			
				Left ventricle	Right ventricle	Pulmonary artery	Aorta
1	L. E.	36	F	0.06	0.08	0.14	0.11
2	L. J.	16	M	0.13	0.06	0.08	0.16
3	M. N.	42	F		0.065	0.09	
4	F. B.	14	F		0.07	0.10	
5	C. G.	19	F		0.09	0.12	
6	B. L.	4	F		0.05	0.08	
7	S. M.	9	M		0.08	0.14	
8	H. J.	4	M	0.06	0.085	0.85	
9	O. H.	28	M		0.065	0.09	
10	T. C.	27	F		0.06	0.08	
11	W. J.	6	F				
12	I. Z.	9	F		0.08	0.12	
13	F. R.	13	M		0.08	0.11	
14	N. M.	17	F	0.10	0.08		0.16
15	C. C.	16	F		0.08	0.12	
16	B. C.	59	M		0.09	0.14	

Right-to-Left Shunt: In comparing the extracardiac (Fig. 1) and intracardiac phonocardiograms (Figs. 9–13) of one of the two cases with right-to-left shunt (case 1), the following observations were made. A short systolic murmur of small amplitude was recorded over the left sternal border, with greatest intensity over the fourth-fifth left interspace. Within the heart, a systolic murmur was recorded in the right atrium, left atrium, and left ventricle, but with the greatest intensity in the left atrium. There was no systolic murmur in the pulmonary artery and right ventricle. The 1st sound was prolonged over the entire precordium. Within the heart, the first part of the 1st sound in the right ventricle occurred 0.08 sec after the Q of ECG and coincided with the closure of the tricuspid valve. The last part of the 1st sound took place 0.14 sec after Q and coincided with the opening of the pulmonic valve. In the left heart, the 1st component of the 1st sound occurred 0.06 sec after Q and coincided with the closure of the mitral valve while the last component of the 1st sound took place 0.11 sec after Q and coincided with the opening of the aortic valve (Table III). Thus, *prolongation of the 1st sound in this case was probably due to a delayed opening of the pulmonic valve.*

The 2nd sound was not split, but prolonged over the precordium. The 2nd sound within the pulmonary artery coincided with the second component of the prolonged external 2nd sound.

A short diastolic murmur of minimal amplitude was recorded within the left ventricle, left atrium, pulmonary artery, right atrium, but no appreciable early diastolic murmur was recorded externally.

A presystolic murmur, not in crescendo, coinciding with the atrial contraction, was recorded all over the precordium with the maximum intensity over the apex. A similar presystolic murmur was recorded in the left ventricle, pulmonary artery and right ventricle with the greatest intensity in the left ventricle.

Discussion

Splitting of the 1st sound[1] is frequently present in atrial septal defect with left-to-right shunt. It has been claimed[2] that this phenomenon is due to an unusually delayed closure of the tricuspid valve followed by delayed opening of the pul-

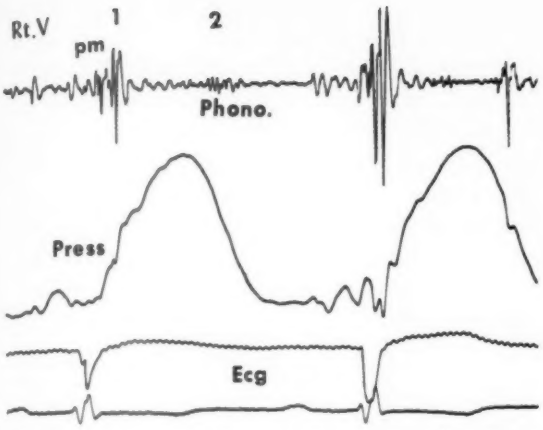

Fig. 10. Case 1. Right ventricle: intracardiac phono (presystolic murmur). Film speed: 100 mm/sec.

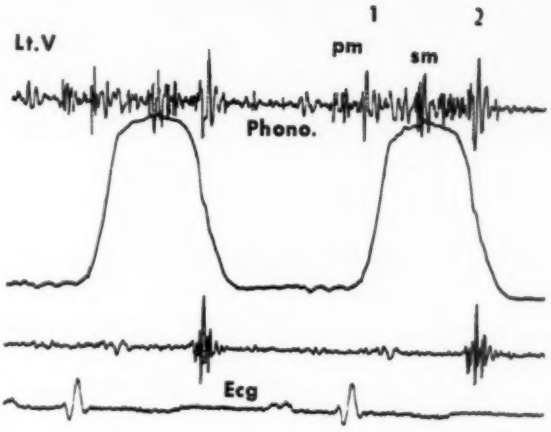

Fig. 11. Case 1. Left ventricle: intracardiac phono (presystolic murmur, systolic murmur, few vibrations in diastole). Film speed: 100 mm/sec.

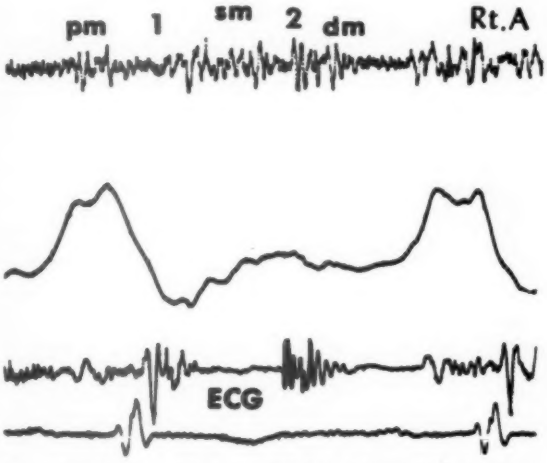

Fig. 12 (above). Case 1. Right atrium: intracardiac phono (systolic murmur, diastolic murmur). Film speed: 100 mm/sec.

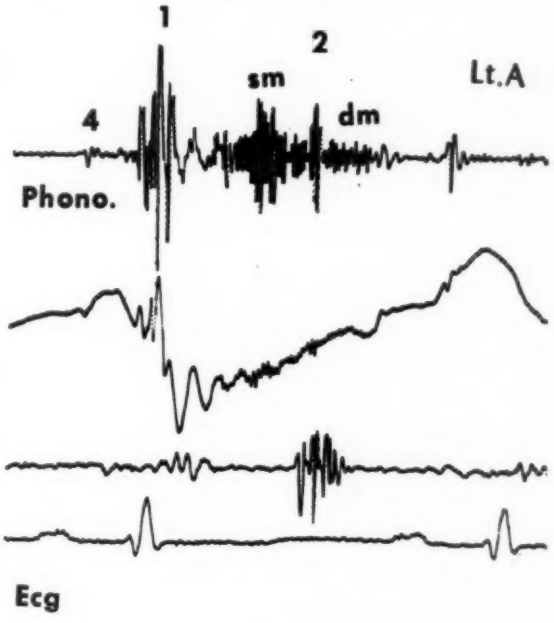

Fig. 13 (right). Case 1. Left atrium: intracardiac phono (4th sound, systolic murmur, diastolic murmur). Film speed: 100 mm/sec.

monary valve, in connection with right bundle branch block.

In a study of intracardiac phonocardiograms and pressure pulses in experimental animals and normal subjects by Luisada *et al.*[9] the four major vibrations of the central phase of the 1st sound were attributed to the subsequent occurrence of four valvular events: closure of the mitral valve, closure of the tricuspid valve, opening of the pulmonary valve, and opening of the aortic valve.

In one case with moderate left-to-right shunt without pulmonary hypertension (case 2), we observed that, in spite of complete right BBB, not only did the tricuspid valve close earlier than the mitral, but even the beginning of ejection of the right ventricle preceded the closure of the mitral valve. It is beyond doubt that in this case, splitting of the 1st sound was due to a considerably *delayed closure of the mitral valve*. The significance of this fact still escapes us and moreover, no rule can be deduced from one case.

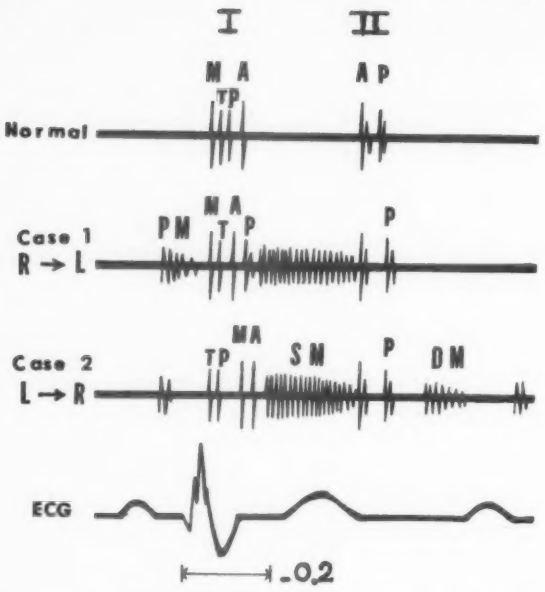

Fig. 14. Sequence of events in two cases studied with both right and left heart catheterization. Case 1 had right-to-left shunt, case 2 had left-to-right shunt. M = mitral; A, aortic; P, pulmonic; T, tricuspid. See text.

In the presence of significant right-to-left shunt and pulmonary hypertension (case 1), the 1st sound was made by vibrations which coincided in sequence with the closure of the mitral valve, closure of the tricuspid, opening of the aortic valve, and opening of the pulmonic valve. Thus, in this case, the prolongation of the 1st sound was due to *delayed opening of the pulmonic valve*, and the right ventricle had a longer diastolic filling time in comparison with the normal.

CAUSES AND SIGNIFICANCE OF THE SYSTOLIC MURMUR

The systolic murmur over the 2nd left interspace found in atrial septal defect has been recognized as a significant clinical sign and was explained by two alternative mechanisms. The first was that of vibrations of the atrial septum during ventricular systole as a result of the shunt. It was difficult to explain why this murmur occurred only during ventricular systole and not during diastole. The 2nd was that of turbulence created by a relative large pulmonary flow (so-called "relative pulmonic stenosis"). Out of five cases with left-to-right shunt, the intracardiac murmur was particularly large within the pulmonary artery in four. This confirms that, in the majority of cases, a flow murmur over the pulmonic area (or a relative pulmonic stenosis) should be admitted. The other case, as well as the only studied case with right-to-left shunt, represents an exception and will be discussed below.

We have shown that in case 1 there was no systolic murmur in either the pulmonary artery or right ventricle. In case 4, only a few systolic vibrations were recorded in the pulmonary artery. However, in both patients, a systolic murmur was recorded over the 2nd left interspace. It is apparent that this systolic murmur originated in other cardiac chambers, i.e., the left and right atrium and the left ventricle in case 1, and the right ventricle and atrium in case 4. Since the intensity of the intracardiac systolic murmur in case 1 was greatest in the left atrium on account of right-to-left shunt, it is reasonable to assume that the systolic murmur over the left 2nd interspace and other areas was mainly transmitted from this chamber, and only partly from the right atrium and left ventricle.

In case 4, the systolic murmur was larger in the right ventricle then in the right atrium. It is reasonable to assume that the systolic murmur over the left second interspace and other areas was mainly transmitted from the two chambers of the right heart.

The second cause of a systolic murmur, a relative pulmonic stenosis, is evident in patients with a large left-to-right shunt. We have shown (case 2) that the systolic murmur recorded in the pulmonary artery was diamond-shaped while that of the right ventricle was in decrescendo. It is possible that they were due to different mechanisms. Since the intensity of the systolic murmur was somewhat larger in the right ventricle than in the right atrium, and the tricuspid valve was closed, it is likely that the decrescendo systolic murmur originated in the right ventricle.

CAUSES OF OTHER AUSCULTATORY SIGNS

A *split 2nd sound* is one of the most common auscultatory signs of atrial septal defect. Our findings agreed with those of others and revealed that the second component of the 2nd sound was always due to a considerably delayed closure of the pulmonary valve.

In a patient with pulmonary hypertension, the 2nd sound was prolonged and large (case 5); the 2nd sound was split only in the 4th left interspace.

A mid-diastolic murmur was recorded in the left ventricle, left and right atrium, and pulmonary artery, in one patient with right-to-left shunt (case 1). The site of formation was probably the left atrium.

In a case with left-to-right shunt (case 6) an early diastolic murmur was recorded in the right ventricle and pulmonary artery, indicating possible pulmonary insufficiency.

A delayed short mid-diastolic murmur was recorded in the right ventricle, right atrium and pulmonary artery in 4 cases, but no diastolic murmur was recorded externally. This mid-diastolic murmur is probably due to relative stenosis of the tricuspid valve, as a result of a large left-to-right shunt.

Finally a presystolic murmur was recorded in the left ventricle, pulmonary artery and right ventricle, both internally and over the apex, second left interspace, and other areas. This presystolic murmur coincided with the atrial contraction. Since this murmur recorded over the precordium was either in decrescendo or of low intensity, it may be easy to differentiate it from that of mitral stenosis.

Conclusions

(1) Intracardiac and external phonocardiograms have been studied in five patients with atrial septal defect with left-to-right shunt and in one patient with right-to-left shunt.

(2) The 1st sound was split in three cases. In one case with left-to-right shunt, the splitting was due to delayed closure of the mitral valve and delayed opening of the aortic valve. In the case with right-to-left shunt, a prolonged first sound was found, due to a delayed opening of the pulmonic valve.

(3) The 2nd sound was usually split on account of delayed closure of the pulmonic valve.

(4) Systolic murmurs are originated in several locations. In cases with left-to-right shunt the systolic murmur was maximal in the pulmonary artery; it was also recorded in the right ventricle and atrium.

(5) A short mid-diastolic murmur seems to originate in the right ventricle as a result of relative tricuspid stenosis caused by the large flow.

(6) A presystolic murmur or a fourth sound was usually recorded in several chambers in connection with the atrial contraction.

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Diagnosis of Septal Defects by the Combined Use of Heart Catheterization and Selective Cinecardioangiography*

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Since July 1955 work has been in progress on the development of a technic for combining heart catheterization with high speed motion picture photography of the passage of contrast media, injected into any of the heart chambers or great vessels, for the solution of diagnostic problems in patients with congenital heart disease.[1] Experience to date indicates that the method may be safely employed with very satisfactory diagnostic accuracy. The purpose of this communication is to describe its application to the precise demonstration of defects in the cardiac septa.

Combining heart catheterization with selective cinecardioangiography has not proved to be more hazardous than either right heart catheterization alone,[2] or conventional venous angiocardiography.[3,4] Of 500 patients with congenital heart disease, ranging in age from 8 days to 49 years, in whom 985 selective injections of contrast media have been made, one death has been, in part, attributable to the procedure. This occurred in a 13-day-old infant with agenesis of the left lung and a large atrial septal defect, who developed apnea followed by cardiac asystole while a routine cut-down was being performed before insertion of the catheter. Postmortem examination revealed a large cerebellar hemorrhage due to birth injury. The mortality rate due to the procedure is therefore 0.2 per cent, but it should be emphasized that no deaths have occurred as a result of nearly 1,000 injections of contrast media directly into either the right or left heart chambers, aorta, or pulmonary artery.

Diagnostic Limitations of Right Heart Catheterization

For longer than a decade, right heart catheterization has been regarded as the safest and most reliable method for proving the presence and location of intracardiac left to right shunts. Comparative measurement of blood oxygen content in the cavae, right heart chambers, and pulmonary artery permitted such shunts to be recognized. It was presumed, usually correctly, that the point where a significant increase in blood oxygen content occurred defined the location of a septal defect. Clinically, utilization of this technic in more than 2,000 patients served to bring out certain failures and limitations which have assumed increased importance since the advent of modern intracardiac surgery. These may be summarized as follows:

(1) Occasionally, in the presence of an atrial septal defect, sampling of blood in the right atrium fails to localize the shunt at the atrial level because of inadequate mixing of left atrial blood in the right atrial chamber. An increased oxygen content is found instead in the right ventricle where more complete mixing occurs, leading to an erroneous diagnosis of ventricular septal defect.

(2) A ventricular defect high in the membranous portion of the septum not infrequently shunts oxygenated blood directly from the left

* From the Cardiac Catheterization Laboratory of the Cleveland Clinic, Cleveland, Ohio.

ventricle across the highest portion of the ventricular septum into the pulmonary artery, leading to an erroneous "physiologic" diagnosis of patent ductus arteriosus.

(3) Anomalous pulmonary venous drainage, partial or complete, to the superior vena cava or right atrium causes a left to right shunt which may be attributed to the presence of a nonexistent atrial septal defect.

(4) A large left to right shunt at the atrial level occasionally obscures recognition of an additional shunt at the ventricular level in patients with coexisting atrial and ventricular septal defects.

(5) The presence of severe mitral regurgitation due to a cleft in the medial leaflet of the mitral valve in patients with large left to right shunts at the atrial level cannot be recognized by pressure measurements or blood oxygen determinations. Closure of such an atrial defect without adequate simultaneous correction of the valve deformity is catastrophic to the patient. Surgical correction of this combination of defects is technically more hazardous and difficult than is correction of uncomplicated atrial defects, even when all such defects are corrected under direct vision, utilizing a pump oxygenator.

(6) In the presence of pulmonic stenosis with an intact ventricular septum, an atrial septal defect capable of producing a large left to right shunt after effective correction of the valve lesion may not be distinguished from a functionally unimportant patent foramen ovale. Either may permit only a right to left shunt at the atrial level, when right atrial pressure is pathologically elevated due to an obstruction in the right ventricular outflow tract.

(7) The true size of an intracardiac communication may not be estimated by measurement of a left to right shunt, since the shunt volume flow is influenced greatly by wide variations in the relationship between systemic and pulmonary vascular resistance. For this reason, large but correctable defects in the membranous portion of the interventricular septum may produce physiologic changes closely identical to those encountered in patients with complete absence of the ventricular septum. Multiple separate defects in the ventricular septum are indistinguishable from a single defect.

Limitations of Venous Angiocardiography

Conventional venous angiocardiography, as an isolated diagnostic method, has presented even greater difficulties in specific evaluation of diagnostic problems involving intracardiac left to right shunts. Because of dilution of contrast media in peripheral veins, large doses have been required to secure satisfactory opacification of intracardiac structures. Such doses, utilized repeatedly at the time of a single study, have been responsible for fatalities which have led to repeated injunctions against multiple injections,[3,5] and to the development of cumbersome and expensive biplane x-ray technics. Injection of contrast media into peripheral veins inevitably causes relatively slow and simultaneous opacification of overlapping right heart chambers, obscuring essential detail. In patients with large shunts, persisting opacification of the right atrium and ventricle often obscures recognition of a left to right shunt, because greatly diluted media returns from the pulmonary circulation to the left heart, with tremendous velocity, before complete clearance of the right heart has occurred. In all such instances, demonstration of a shunt depends on re-opacification of the right atrium, ventricle, or pulmonary artery. If right atrial re-opacification is well demonstrated, it is impossible to recognize a coexisting shunt at the ventricular or pulmonary artery level. Only rarely is re-opacification of a chamber clearly enough defined to permit exact localization and demonstration of the size of a defect in the atrial or ventricular septa. In the uncommon instance where such demonstration is attained, adequate evaluation of the functional stress caused by the defect is limited, since this is best defined by appropriate pressure and flow measurements.

Combined Cardiac Catheterization and Cinecardioangiography

The availability of dependable fluoroscopic image intensifiers* has greatly simplified the

* North American Philips Company, Incorporated, New York, New York.

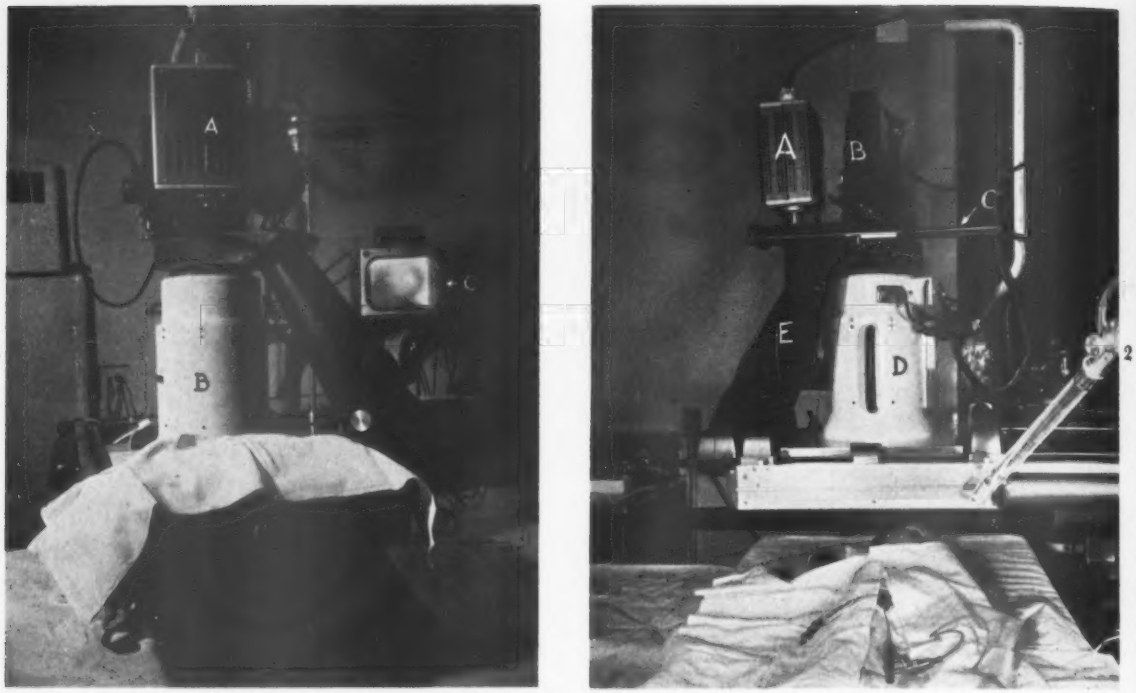

Fig. 1. Television vidicon camera (A) mounted above image intensifier (B) transmits fluoroscopic image by coaxial cable to closed circuit television receiver, (C) which may be observed in a well lighted room during cardiac catheterization by all members of the team.

Fig. 2. Television (A) and 35 mm motion picture (B) cameras are permanently fixed in a sliding mount (C) above image amplifier (D). This permits instant change from fluoroscopic viewing of image with television camera to permanent photographic recording at rate of 54 frames per sec. During 35 mm photography the optical periscope (E) permits operator to observe events being recorded by the camera. The sliding camera mount rotates 360° around the vertical axis of the image amplifier, permitting the head of the patient to be placed at either end of the table.

problem of combining heart catheterization with contrast visualization of intracardiac structures to overcome the difficulties described above. The brightness of the fluoroscopic image is increased more than 1,000 times by the use of the image intensifier, producing an image bright enough to be photographed by a television vidicon camera, using less than one-half the x-ray energy required for conventional fluoroscopic study. This permits routine catheter manipulation to be comfortably observed by all members of the catheterization team on an appropriately positioned closed circuit television receiver* (Fig. 1) in a well lighted room. Permanent photographic recording of any desired portion of a study may be made by shifting a 35 mm motion picture camera, mounted beside the television camera into position over the image intensifier (Fig. 2). The shift from television to optical photography requires less than ten seconds.

* Dage Television Division, Michigan City, Indiana.

This equipment makes it possible, at any time during heart catheterization, to make selective injections of contrast media into any of the heart chambers, and photograph the passage of the media through the central circulation. Using Eastman Tri-X film, it has been possible to photograph these injections routinely at 54 frames per second, with individual exposures of 9.2 milliseconds. Because the factor of dilution in the peripheral venous bed is avoided, excellent contrast visualization is achieved in children with maximal individual doses of 0.5 cc of 90 per cent Hypaque/lb body weight. For patients weighing more than 100 lb, single doses have been limited to 30 cc, regardless of body mass. By limiting the size of individual injections it has been possible to make multiple injections into one or more heart chambers, allowing 15 to 20 min between each injection to permit renal clearance of previously injected media. Increasing experience

indicates that if a single injection of this size is well tolerated, two or even three additional injections may be made with safety during the course of a single study.

Although the photographic quality of individual 35 mm motion picture frames does not equal that achieved in properly exposed full size x-ray films, the ability to study such motion picture film in "slow motion" by projection at 12 to 16 frames per second, supplemented by analysis of individual frames, permits more certain anatomic diagnosis than has ever before been possible. Unfortunately such *motion* study cannot be satisfactorily reproduced for journal or textbook presentation, and it is inevitable that "still" enlargements of individual motion picture frames, as reproduced herein, will not compare favorably with reproductions of life-sized x-ray plates made by the best available high voltage and current technics. It must be emphasized that this esthetic limitation is of minor importance compared to the practical advantages gained by slow motion study of extremely rapid intracardiac phenomena.

Procedure and Clinical Applications

In order to define the infinite variety of congenital lesions that may be encountered, heart catheterization should not be performed as a sharply routinized procedure, but is best employed as a flexible intracardiac exploration. In the study of suspected congenital lesions, the best approach to the heart is by way of the inferior vena cava, since this permits complete exploration of the interatrial septum. In more than 50 per cent of the last 500 patients with congenital heart disease studied in this laboratory, catheterization of the left heart chambers has been possible by way of a patent foramen oval or an atrial septal defect. This permits pressure and blood oxygen measurements in the left atrium, pulmonary veins, and left ventricle, as well as selective injections of contrast media into the left atrium, left ventricle, or both.

Left Atrial and Ventricular Catheterization: After blood oxygen determinations have been made in the cavae and right atrium with a cuvette oximeter, the atrial septum is carefully explored with the catheter tip. Almost invariably, if a left to right shunt is demonstrated at the atrial level, easy passage of the catheter across the atrial septum into the left atrium can be accomplished. In a large number of patients in whom a measurable shunt is not recognized, it is also possible to enter the left atrium, usually by way of a foramen ovale, or less frequently, through a true atrial septal defect, unrecognized by blood oxygen determinations. After blood oxygen and pressure measurements have been made in the left atrium and one or more pulmonary veins, the catheter tip is passed across the mitral valve into the left ventricular chamber. This has not proved to be a difficult technical problem, and is now accomplished in more than 85 per cent of patients in whom left atrial catheterization is possible.

The electrocardiogram is carefully monitored during left ventricular catheterization. Usually a few premature ventricular beats, which quickly subside, are observed during manipulation of the catheter tip across the mitral valve into the left ventricular apex. Occasionally, repetitive ectopic ventricular beats occur, technically constituting a short run of ventricular tachycardia. In every such instance, this has been promptly abolished by withdrawing the catheter a fraction of an inch, and has not required displacing it back into the left atrium. It must be emphasized, however, that failure to promptly recognize and abolish a ventricular tachycardia because of inadequate electrocardiographic monitoring might easily lead to a persistent ventricular arrhythmia and disaster.

Selective Opacification of Left Ventricle

After pressure and blood oxygen determinations have been made, selective opacification of the left ventricle is routinely performed. The passage of contrast media is permanently recorded on 35 mm motion picture film and is simultaneously observed by the operator through a periscope lens system (Fig. 2), which functions as an optical "finder" during motion picture photography. Although the media is very rapidly dispersed, it is usually possible to immediately recognize the presence or absence of gross lesions. The fleeting impression obtained usually provides welcome information, which may modify the further course of a

study, but under no circumstances should it be considered a potential substitute for permanent photographic recording.

Ventricular Septal Defect: In most patients the plane of the ventricular septum is best visualized when the patient is rotated 60 to 70 degrees into the left anterior oblique projection. Direct opacification of the left ventricular chamber in this projection will precisely define the location and relative size of a defect in the ventricular septum which may coexist in a patient with an atrial defect, but be unrecognized by blood oxygen determinations (Fig. 3). Multiple de-

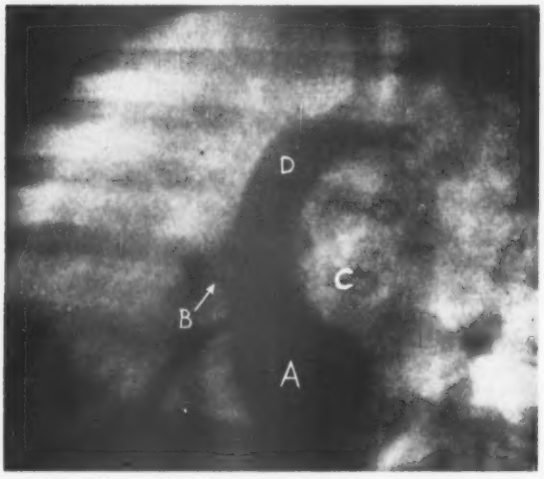

Fig. 3. Cinecardioangiogram in L.O.A. projection. Selective opacification of left ventricle (A) in a patient with a large interatrial septal defect demonstrates a small defect (B) in the membranous portion of the interventricular septum. Note absence of regurgitation of contrast media into left atrium (C). Muscular portion of the ventricular septum is intact. The aorta (D) arises normally from the left ventricle.

fects in the ventricular septum are easily recognized (Fig. 4), as is congenital absence of the septum (Fig. 5). When inadequate mixing of a shunt at the atrial level prevents recognition of an atrial defect, but appears to support the presence of a left to right shunt at the ventricular level, demonstration of an intact ventricular septum (Fig. 6) by this technic has so far proved to be absolutely dependable.

Mitral Insufficiency: The presence of severe mitral insufficiency in patients with large atrial septal defects is easily recognized by massive reflux of contrast media from the left ventricle into the left atrium (Fig. 7). The coexistence of mitral insufficiency with an atrial defect may be excluded from consideration as a diagnostic possibility if the left atrium is not opacified during left ventricular injection (Fig. 3, 4, 6). Occasionally faint artifactual opacification of the left atrium is momentarily seen during left ventricular opacification, due to displacement of the mitral valve by the catheter. This has been encountered in fewer than 20 per cent of patients with normal mitral valves, and is usually easily recognized during analysis of the motion pictures by the small volume of the regurgitant stream, and by the fact that it almost invariably occurs during a long ventricular diastolic pause following a premature ventricular beat.

SELECTIVE OPACIFICATION OF LEFT ATRIUM

Atrial Septal Defect: When left ventricular study is complete, the catheter is withdrawn to the left atrium and selective opacification of this chamber is performed. An atrial septal defect is usually best demonstrated by injection of contrast media into the left atrium or its appendage with the patient rotated 20 to 30 degrees into the left anterior oblique position. In this projection the rounded interatrial septum is visualized above and medial to the more linear and inferior plane of the ventricular septum. An atrial septal defect demonstrated by this method is seen in Figure 8.

Atrial Septal Defect in Pulmonic Stenosis: If the communication by which the catheter has reached the left atrium is a foramen ovale, with an adequate valve preventing a left to right shunt, media injected into the left atrium does not cross the atrial septum (Fig. 9). This technic has been particularly valuable in patients with a right to left shunt at the atrial level due to pulmonic stenosis with intact ventricular septum. If the atrial communication is capable of permitting a left to right shunt, it will be demonstrated by transient opacification of the right atrium due to momentary overdistention of the left atrium during selective left atrial injection. When this occurs the atrial defect should be closed at the time of pulmonary valvulotomy. If it does not occur, the atrial communication may be disregarded

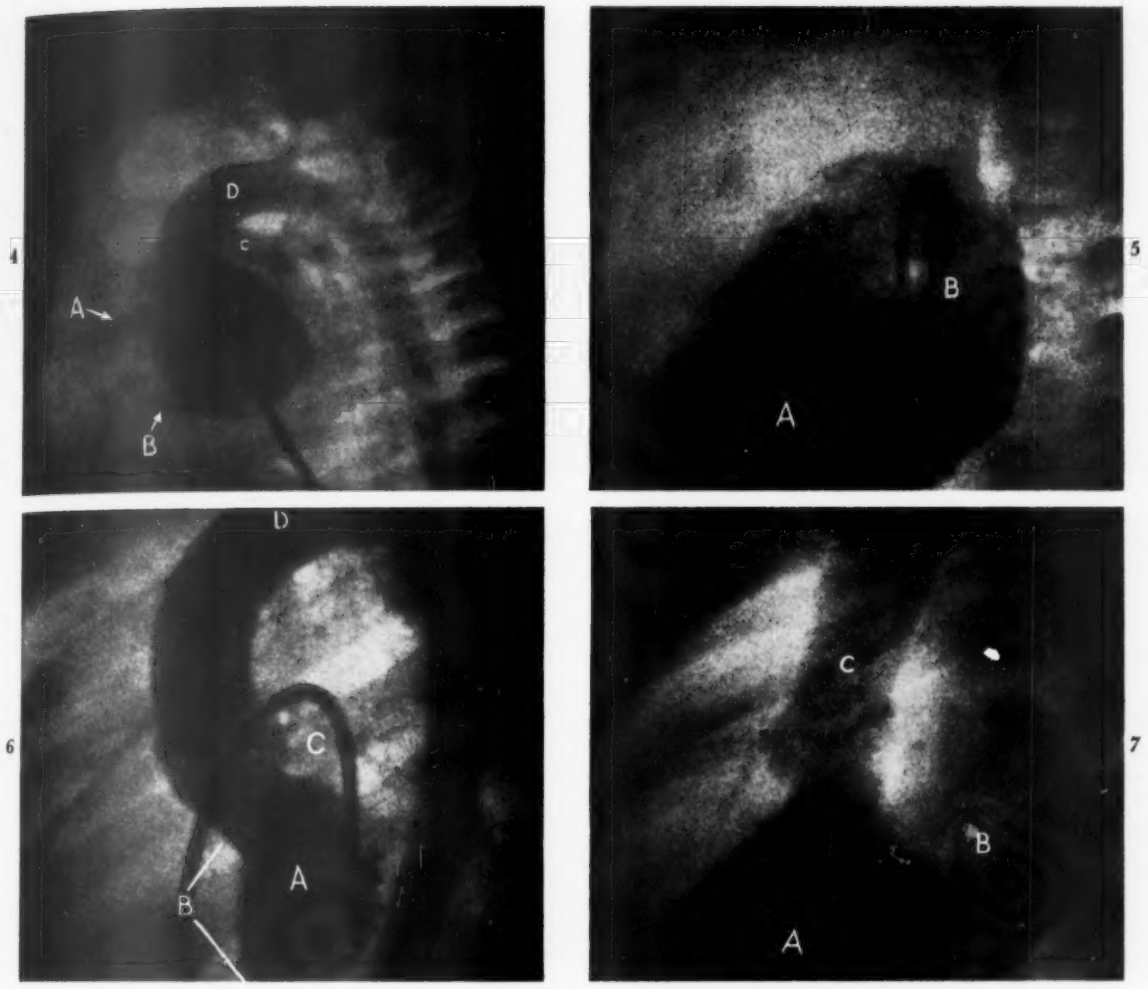

Fig. 4. Cinecardioangiogram in left lateral projection demonstrating multiple ventricular septal defects. Injection of contrast media into left ventricle demonstrates separate coexisting defects in the membranous (A) and muscular (B) portions of the interventricular septum. There is no mitral regurgitation. The bifurcation of the pulmonary artery trunk is seen (C) above the left ventricle below the aortic arch (D).

Fig. 5. Cinecardioangiogram (L.O.A. projection). Selective opacification of left ventricle reveals complete absence of ventricular septum. A common ventricular chamber is opacified (A) with reflux of contrast media into the left atrium (B) across an incompetent A-V valve.

Fig. 6. Cineangiocardiogram in L.O.A. projection in atrial septal defect. Selective opacification of left ventricle (A) demonstrates an intact interventricular septum (B). There is no regurgitation of contrast media into the left atrium (C) despite the fact that catheter crosses the mitral valve. The aortic arch (D) is normal. This patient had an uncomplicated atrial septal defect, but blood oxygen determinations indicated a left to right shunt at the ventricular level, because of inadequate mixture of left atrial blood in the right atrium.

Fig. 7. Cinecardioangiogram in L.O.A. projection in patient with large interatrial septal defect and mitral regurgitation. Selective opacification of left ventricle (A) demonstrates massive regurgitation of contrast medium into left atrium (B), due to mitral regurgitation. The ventricular septum is intact. The small ascending aorta (C) arises normally from the left ventricle.

since it will not produce a left to right shunt after successful pulmonary valvulotomy.

Anomalous Pulmonary Venous Drainage to the Superior Vena Cava or Right Atrium: This condition should be suspected whenever a left to right shunt is demonstrated at the atrial level and the left atrium cannot be catheterized by the technic described above. This problem should also be considered when a bidirectional shunt is demonstrated at the atrial level in patients who do not present evidence of pulmonary or tricuspid valve obstruction. When

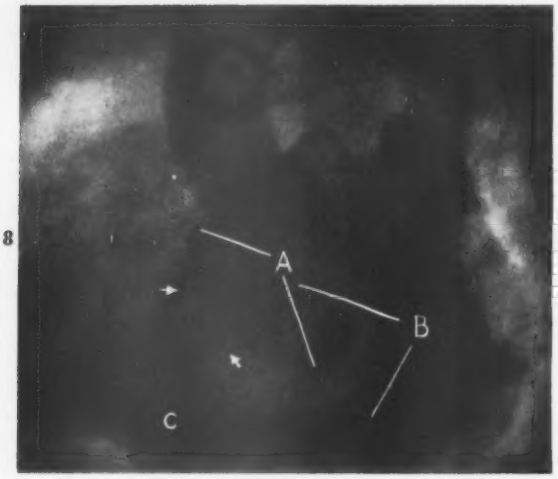

Fig. 8. Cinecardioangiogram in atrial septal defect. Injection into left atrium with patient rotated 35 degrees into L.O.A. projection. The rounded plane of the atrial septum (A) is seen above and medial to the linear plane of the ventricular septum (B) during ventricular systole. A jet of contrast media crosses the atrial septum (arrows) to opacify the right atrium (C), demonstrating a large interatrial septal defect.

Fig. 9. Cinecardioangiogram (L.O.A. projection) in patient foramen ovale without left to right shunt. Injection into left appendage (A) opacifies left atrium (B) and ventricle (C). No contrast media crosses atrial septum, proving the communication by which catheter was passed into left atrium is a foramen ovale with an adequate valve. The ventricular septum is intact.

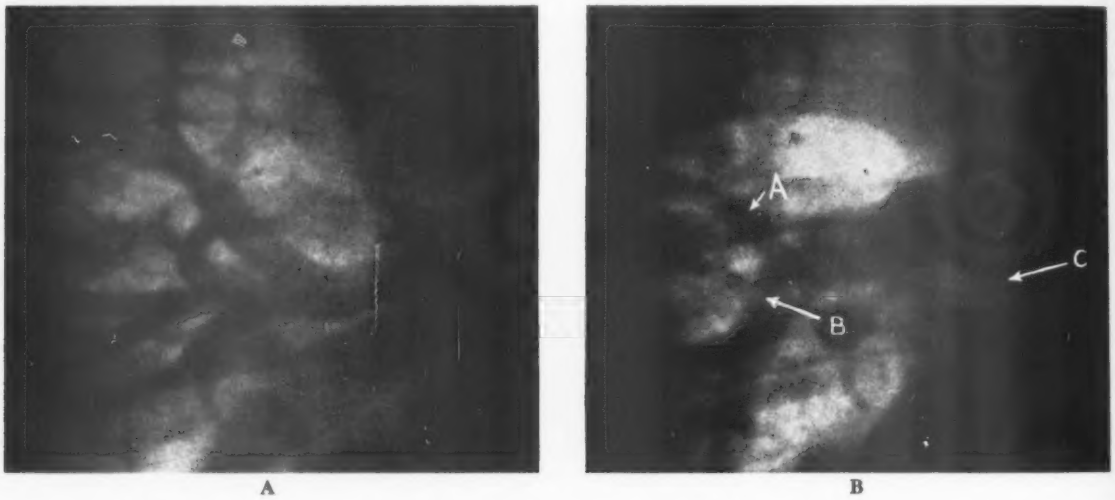

Fig. 10. Cinecardioangiogram in patient with anomalous pulmonary venous drainage. (A) Opacification of the right pulmonary artery. (B) Exposure two seconds later. Pulmonary venous drainage from right upper (*A*) and middle (*B*) lobes returns to superior vena cava (*C*).

this problem is encountered, careful exploration of the proximal superior vena cava and right atrial chamber will often permit direct catheterization of the anomalous pulmonary veins. If direct catheterization of such veins cannot be accomplished, pulmonary venous return may be demonstrated by injection of contrast media into the pulmonary artery with the patient in the P-A projection. Anomalous pulmonary venous drainage of the right upper and middle pulmonary veins into the superior vena cava is shown in Figure 10.

In infants and children weighing less than 70 lb, the technics described have proved to be consistently dependable. Their utilization in patients of large body mass is relatively limited by the small field size of presently available image intensifying screens. It is

anticipated that the development of larger intensifying screens in the near future will improve effective application of these technics to the problems encountered in adults with congenital and acquired cardiovascular lesions.

Summary

Heart catheterization has been combined with selective cinecardioangiography as a single diagnostic procedure for definitive evaluation of congenital heart lesions.

In practical application, the combined technic has proved to be no more hazardous than either conventional angiocardiography or right heart catheterization.

An image intensifier has been used to permit high speed motion picture photography of the fluoroscopic image. Small quantities of contrast media, injected into either right or left heart chambers, have been photographed at rates of 54 frames per second to precisely define lesions of the cardiac septa.

The technic of selective opacification of the left atrium and ventricle has been used to demonstrate:

(1) Patent foramen ovale.

(2) Uncomplicated atrial septal defect.

(3) Atrial septal defect and coexisting ventricular septal defect.

(4) Atrial septal defect with mitral regurgitation.

(5) Multiple ventricular septal defects.

(6) Single ventricle with regurgitation across a common A-V valve.

(7) Anomalous pulmonary venous drainage to the superior vena cava.

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Surgical Treatment of Atrial Septal Defects

Open Versus Closed Technics*

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FIFTY-EIGHT patients with atrial septal defects have now been operated upon since March 1952. In the first 36 patients "closed technics" were employed.[1] The last 22 patients have had repair of their defects under direct vision, utilizing extracorporeal circulation with a rotating disc oxygenator.

The early papers on the surgical treatment of atrial septal defects dealt primarily with their anatomy, physiology, hemodynamics, clinical course, and pathology. From this material evidence was demonstrated as to the advisability of operative intervention. The operative morbidity and mortality during this developmental period were acceptable. There were two deaths in our 36 patients using the "closed technic." Both of these deaths occurred early in our experience in patients with severe pulmonary hypertension. As a consequence, we advised against operation in patients with severe pulmonary hypertension.[2] Initially, operation was performed only in those patients incapacitated from their defect or who had considerable cardiac enlargement and increased pulmonary vascularity. It is now obvious that such patients, even though operation was desirable, were frequently beyond the opportune time for operative intervention. We now feel that surgical repair of the defect is indicated when catheterization studies show a significant shunt flow. Operative intervention need not be delayed until the patient becomes symptomatic. Patients with atrial septal defects do not show a comparable early rise in pulmonary artery pressures in contradistinction to patients with a ventricular septal defect, even though their pulmonary blood flow may be as great or greater. It is true that occasionally such changes may be seen in the early years of life but usually they develop later.

The benefit derived from complete closure of the defect is readily apparent. Many technics have been presented during the past regarding the efficacy of closure using both "closed technics"[3–6] and direct vision employing hypothermia.[7–8] Postoperative catheterization studies by all groups report a varying incidence of incomplete closures. In our series, postoperative catheterization studies have revealed that three of 14 patients studied still showed a left to right shunt. It is true that for the most part only those patients still having signs or symptoms of a persistent defect were catheterized. Most of these patients had defects in the inferior-posterior segment of the septum, below or adjacent to the tricuspid valve but in some the defect was more centrally located. Re-operation in three of these patients has shown only strands of tissue within the defect. Because of this discouraging high incidence of incomplete closures, all patients with an atrial septal defect are now operated upon by the open, direct vision technic by means of a mechanical pump oxygenator. Even though some operators have reported a better postoperative result than others using closed technics, it is obvious in closing such defects under direct vision that unless sutures are placed every 1 to 2 mm that shunting of blood will occur. Residual openings in the septum can be visualized which allow considerable shunting of blood which would or could not be detected by the palpating finger. There is an advantage in the use of extracorporeal circulation over

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hypothermia in that such operations can be performed in an unhurried manner and are associated with fewer complications.

Results

Twenty-two patients with atrial septal defects have now been repaired under direct vision with the use of a rotating disc pump oxygenator, with only one death. This disproves the argument of the advocates of closed methods that the operative mortality with extracorporeal circulation would be unreasonably high. With the right auricle open and the various anatomical features of the atrial septum easily visualized, care can be exercised in avoiding the atrioventricular node and in no instance has there been interference with this node or nerve bundle leading to conduction defects or heart block. Furthermore, one has ample time and exposure to repair more difficult anomalies such as atrioventricularis communis and anomalous pulmonary venous drainage, which is not true when operations are done by closed technics or under hypothermia.

Postoperative catheterization studies are now being performed routinely from six months to one year on all patients with atrial septal defects which have been closed under direct vision. Of the 12 patients studied so far, all have shown complete closure of the defect. It is also of interest to note that the pulmonary artery pressures have all returned to normal concomitant with reduction in heart size. All have shown improvement in the electrocardiogram as compared to only six in which this occurred in the initial group operated upon by closed technics even though it would appear that their defect was closed. The average preoperative pulmonary artery pressure in the direct vision closure group was 45 mm Hg as compared to 26 mm Hg postoperatively.

Analysis of Patients

Pulmonary Artery Pressure: For this discussion, only those patients operated by the open technic will be considered. The age range varied between 3 to 42 years of age. Eleven of the patients had right ventricular or pulmonary artery pressures above 40 mm Hg and six ranged between 35 to 40 mm Hg. The other four were below 35 mm Hg. The older patients had the higher pressures which suggests that with the increasing duration during which the increased pulmonary shunt flow existed there was resultant increased pulmonary vascular sclerosis and resistance. The fact that all of the pressures returned to normal range postoperatively suggests that the pulmonary vascular resistance in this group is not fixed but may be reversible over a period of a year's time. Six of the patients had a differential pressure over the pulmonary valve averaging 17 mm Hg which at the time of surgery was found to be due to a relative pulmonary valvular stenosis resulting from dilatation of the right ventricle and pulmonary artery with a fixed pulmonary valvular annulus. Postoperatively with correction of the increased shunt flow and reduction in the size of the right ventricle and pulmonary artery this pressure differential has corrected itself.

Four of the patients had partial anomalous pulmonary venous drainage which was easily corrected at the time of surgery by either incorporating the ostia of the pulmonary veins into the septal closure or by utilizing an Ivalon patch in one instance.

Technic: A right-sided anterolateral exposure was employed in all instances. In the majority of the patients the incision was extended across the sternum. There has been no postoperative complication or increased morbidity from transecting the sternum. The superficial femoral artery was used in all instances as the site of the inflow catheter. This artery is considerably more accessible than the subclavian and is not associated with a postoperative Horner's syndrome as is frequently seen when the subclavian artery is used. The artery is repaired following removal of the cannula with re-establishment of the femoral circulation. Flow rates varied from 60 to 100 cc/kg/min. From 6 to 10 units of fresh blood were used to prime the machine and for blood replacement during the operative procedure. An accurate accounting of the blood balance is maintained both during the run as well as postoperatively. In only one instance was there a bleeding tendency afterward and this occurred in the one early death in the series. This was the first patient operated upon. This patient may have had a blood

idiosyncrasy in that another member of the family also had a bleeding tendency even though no abnormality could be detected from preoperative studies.

During the run there was constant monitoring of the venous and arterial pressure, blood balance, electrocardiogram, electroencephalogram, oxygen saturation, oxygen tension, and carbon dioxide tension. There was intermittent monitoring of blood buffer base, pH, hemoglobin, and hematocrit.

Postoperative Course: Postoperatively the patients are cared for in a special postoperative cardiac recovery section until their discharge. This section is equipped with all the essential facilities to handle any eventuality that might occur and is staffed with the same highly specialized nursing personnel. The postoperative convalescence in this group was remarkably uneventful. The convalescence in the three patients who had had previous operations by the closed technics was gratifyingly less severe with their second operation than with their first. This was undoubtedly due to the fact that the defect was completely closed. All of the patients showed electrocardiographic evidence of increased loading of the left auricle with closure of the defect but in no instance was there any suggestion of left ventricular failure.

Summary

Twenty-two patients with atrial septal defects have now been operated on by the direct vision technic utilizing the rotating disc oxygenator. The operative morbidity and mortality has been less than when closed technics were employed. Postoperative catheterization studies have demonstrated the superiority of the open technic in that all patients so far studied have shown complete closure of their defects.

Addendum

Thirty-two patients with atrial septal defects have now undergone direct vision closure with no additional mortality.

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Seminar on Ballistocardiography

Guest Editor

SIDNEY R. ARBEIT

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The Relation of the Ballistocardiogram to Cardiac Function*

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IN THIS presentation I shall discuss the relationship between ballistocardiograms and cardiac functions. Two preliminary remarks are necessary to clarify my presentation. First, when I speak of ballistocardiograms without qualification, I shall refer to the force ballistocardiograms, records secured either by recording displacement from a high-frequency instrument or by recording acceleration from an ultra-low frequency instrument,[1-3,13] for I have had far more experience with these records than with any others. Second, under the stimulus of these new methods, we must begin to think of the cardiac dynamic functions in a more exact way than clinicians have been accustomed to do. These functions are perhaps best divided into three aspects: those associated with displacement of the blood, such as the stroke volume; those associated with blood velocity, such as the work performed for this is estimated from blood velocity; and those associated with acceleration, the forces.

The ballistocardiogram is obviously directly related to movements of the body's center of gravity, an aspect which has especially interested physicists,[2,3,13] who have made great progress in reducing the errors of the record. The force ballistocardiogram is the second derivative of this displacement; but such a conception is not enough for clinicians, who can scarcely conceive of the center of gravity becoming abnormal in disease. But this movement of the center of gravity is due to the activity of the heart, and the relation of the record of this movement to cardiac function is of vital concern to clinicians. The purpose of this presentation is to review the present state of our knowledge of this subject.

THE THEORETIC APPROACH

As soon as I found, in 1936,[4] that I could secure highly reproducible ballistocardiograms, easily calibrated in terms of force, I was challenged to account for the record and to determine whether our findings were consistent with other quantitative knowledge of the circulation. In a calculation published with Rawson[5] in 1941, I assumed that the contour of the human cardiac ejection curve was similar to that found in certain experiments on dogs, divided the blood mass in the heart and great vessels into units of 10 cc each and calculated the forces involved in starting and stopping each unit. When this array of forces was aligned in time, the time course of their resultant did look very much like a ballistocardiogram. Indeed, the quantitative agreement was as good as could be expected considering the doubtful character of some of the assumptions. And today I find it amusing to note that my first theoretic force ballistocardiogram, which lacked a definite K wave, looks much more like the normal record secured from a modern instrument than like the records I was getting at that time, a fact that I am proud to point out as evidence of the disinterested character of the study. For this reason I have reproduced this first theoretic force ballistocardiogram in Figure 1 of this paper.

Recently Noordergraaf has approached the same subject in another way which has certain advantages over the method I employed, and

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this will be described in another part of this seminar (p. 748). Carried further into diastole than my 1941 study, and so taking account of blood movement in the periphery, the ballistic complex occurring early in diastole is accounted for in Noordergraaf's theory by movement of blood in the arteries of the legs. Both Noordergraaf's recent study and my own earlier one agreed that the forces originating from the left ventricle make a much larger contribution to the recorded ballistocardiogram than did those originating from the right. Experiments such as those recorded in Figure 2 also support this conception.

Fig. 1. A redrawing of the original theoretic ballistocardiogram published in 1941. It bears an extraordinarily close relationship to the normal record secured by ultra-low frequency ballistocardiographs today.

There seems no doubt, therefore, that ballistocardiograms can be logically accounted for and that what we find is consistent with other information about the heart's function. Also, such calculations emphasize one aspect which is essential to an understanding of the field. As a result of cardiac activity, forces manifest themselves which are opposite in direction and so cancel themselves out within the body without causing movement of the body in space. The force ballistocardiogram is not a record of the cardiac force but of the resultant of the cardiac forces. If the heart consisted of a single chamber which discharged into a straight, rigid tube the exact measurement of its forces and the other aspects of its activity by the ballistocardiograph would be easy. To get more information about the relation of ballistocardiograms to the different aspects of the heart's performance, we turned to experiment.

The Experimental Approach

Let us discuss general relationships first.

Relation to Cardiac Stroke Volume: That cardiac stroke volume would somehow be related to the amplitude of the ballistocardiogram was evident to Yandel Henderson and the problem has excited interest ever since. In situations known to be accompanied by increased cardiac output, such as after exercise, during excitement, after adrenalin and in hyperthyroidism, the ballistocardiogram is usually found to be abnormally large; in situations such as myxedema where the cardiac output is small, the ballistocardiogram is also small. The details have been well covered by Nickerson in another section of this seminar devoted to this relationship. My own work[4,6] suggests that the relation is a limited one, quite close when the ballistocardiogram is normal in form, but when the ballistocardiogram is distorted, the empirical formula giving best results when the flow is normal seriously underestimates the stroke volume. Therefore, I was never encouraged to use my method in the clinic where so many of the patients have abnormal records.

The relationship to stroke volume is being studied once more in the laboratory of Professor Klensch, at Bonn, with some very interesting results.[7,8] His use of the record of the displacement of the center of gravity,[8] the second integral of the force ballistocardiogram, as the starting point of the estimate, impresses me as theoretically advantageous, although I have always feared the practical disadvantages which accompany any method that requires ignorant subjects to hold their breath while the record is taken, as they cannot be depended upon to hold it in the same manner twice.

Relation to Cardiac Work: To estimate cardiac work, according to Newton's definition of work, one needs both the pressure and the flow of cardiac ejection at every instant. To secure these curves, and to test the relation between the ballistocardiogram and this aspect of cardiac

function, experiments were undertaken in which cardiac function was simulated in cadavers.[9] In these experiments widely differing amounts of blood (or water) were injected into the aorta and pulmonary artery under many different conditions of blood pressure and vascular elasticity.

In such experiments the work performed on the aortic blood could be estimated with accuracy.[9] When this work is compared with the product of the amplitude or area of the I and J waves of the corresponding ballistocardiograms and the mean blood pressure, the correlation is very strong, the correlation coefficients ranging from 0.82 to 0.88. Obviously, therefore, one can expect to estimate cardiac work from the ballistocardiogram and blood pressure with reasonably good accuracy. But there are difficulties and limitations with the use of such a method in the clinic. While the forces producing ballistocardiograms during life are derived chiefly from the left side, to use the amplitude of this record and the systemic blood pressure to get an estimation of work is far from ideal, for in certain abnormal conditions the proportional contribution of the right side to the amplitude of the ballistocardiogram might well change, and this would interfere with the accuracy of the estimate of left ventricular work.

Relation to the Cardiac Forces: Data secured in the cadaver experiments support the conception that the amplitude of the ballistocardiogram is primarily related to the cardiac forces.[10] The correlation with the integral of the acceleration of the injected blood is improved by taking the square root of the amplitudes or areas of the I and J waves and still further improved by adjusting for the differences in size of the subject. By such means a correlation of 0.92 was secured, a relation so good that the known errors seem adequate to account for the scatter which remains.

Contour Relationships: It often pays to start by oversimplifying a problem in order to be able to solve it at all. Here I must mention briefly the conception that the ballistocardiogram is closely related to the derivative of the cardiac forces,[11] estimated not with infinitesimals, but with a time value which represents the time required for each particle of blood to travel from heart to aortic arch. At the present state of our knowledge such ideas are hardly more than hints, but they may well provide valuable hints regarding the aspects of the ballistocardiogram most likely to correlate empirically with the various higher dynamic functions of the heart, and they also make a start toward a mathematical theory which will altogether explain the ballistocardiogram in terms of cardiac function. This aim assumes that certain cardiac and noncardiac factors causing distortion of the record can be avoided or allowed for. Let us now consider what these might be, and what we know about their magnitude. Those factors having to do with instrumental error are covered elsewhere in this series of papers and I will confine myself to a discussion of the physiologic sources of error.

FACTORS WHICH MIGHT DISTORT THE RECORD

The body is composed of material of varying density and elasticity, the parts some tightly, some loosely bound to one another. This does not provide an ideal system for the transmission of the forces which originate deep in its interior to the instruments we must place outside it. Therefore some distortion seems inevitable. It is obviously essential to learn as much about this as possible, and so I attacked the problem from the experimental viewpoint.

Effect of the Size of the Subject: It must not be forgotten that when one uses the ultra-low frequency instrument the size of the subject is a factor in the interpretation of the amplitude of all records, unless a technic such as that we ordinarily use is adopted. We calibrate with a known force while the subject is on this type of ballistocardiograph, and by adjusting the amplification, bring the deflection caused by standard force to the same value for all subjects. Only under such circumstances can inspection give meaning to the amplitude of ultra-low frequency records in terms of absolute values of cardiac function.

In records from high-frequency ballistocardiographs, differences in the size of the subjects should not theoretically enter into the interpretation of the records. However, results[12] secured in cadaver experiments show that body size does have a slight influence, for the correla-

tion between maximal injection velocity and the ballistic amplitude is significantly improved by an adjustment for differences in the surface area of the subjects tested.[10] The larger the subject, the smaller the ballistocardiogram which results from a given force. However, the size of the correction factor is so small we do not bother with it in routine work at this time.

Nevertheless the cadaver experiments show one thing clearly. As we take our records there is a threshold, that is, a minimum, below which the cardiac forces are not recorded by the ballistocardiogram. And when the cardiac forces do move the body there is loss on the way out, by "impedance," which is in the body rather than in the instrument, and there is greater impedance in larger bodies than in smaller ones. But the threshold is so low and the impedance so small, or so uniform, that both can be neglected in clinical work at this time.

Effect of the Height of Blood Pressure: In the cadaver preparations we performed pairs of experiments in which the energy which simulated systole was kept constant while the blood pressure was made very different.[12] It was only with much difficulty that we were able to demonstrate that such differences in blood pressure had a significant effect on the resulting ballistocardiogram. In the data secured on subjects perfused with blood the effect of differences in blood pressure was not significant, but by adding selected pairs from the experiments in which water was used, and in which higher hypertensions had been secured, a significant effect was demonstrated. The higher the blood pressure the smaller the amplitude of the ballistocardiogram, probably because the increased pulse wave velocity at higher pressures is accompanied by a greater overlapping of the headward and footward forces and so of a diminution in the size of their resultant. But again the effect is a small one, the regression equation showing that a 30 mm Hg increase in diastolic pressure would be the cause of a 10 per cent decrease in ballistic amplitude. This is certainly a fact to be kept in mind, but the influence of differences in pressure seems too small to warrant much attention in the present state of our knowledge.

Effect of Arteriosclerosis: Among the subjects in the cadaver experiments was one who was extremely arteriosclerotic. In this subject the blows of standard energy, used to simulate systole, caused slightly larger ballistocardiograms than in our other subjects.[12] We also had several other subjects in whom the arteriosclerosis was severe, but not extreme, and still others in whom it was moderate or mild, as well as subjects altogether free of such lesions. Only in the first subject could any significant difference be demonstrated which might be due to the arteriosclerosis. So, in our experience, an effect which might be attributed to arteriosclerosis has manifested itself only in one case so extreme that its like would be encountered very rarely in the clinic.

Effect of Asynchronism of the Two Sides of the Heart: A certain amount of such asynchronism is probably within normal limits, the right heart often starting to eject before the left because of the much lower pressure which opposes its ejection. But in disease it seems obvious that one side of the heart, if abnormally weak, might expel its blood so that the maximum of its forces appeared much later than that of the other side. If the asynchronism is small the results of experiments, reproduced in Figure 2, show that the effect manifests itself chiefly by broadening and notching of the J wave, a change which markedly reduces the amplitude of the wave at its tip, but which has little or no effect on the area of the wave. This is one of the many reasons for our preferring to use wave areas rather than wave amplitudes in judging cardiac function. If the asynchronism is greater the J wave may be deeply split, as is shown in Figure 2.

Effect of Movement between the Subject and Table: This source of trouble, which confused especially the diastolic part of the old high-frequency table records, will be dealt with in other parts of this seminar. The modern ultra-low frequency instruments altogether avoid it while attention to tight fixation of the body to the table minimizes the difficulty for the newer high-frequency technics.

OTHER POSSIBLE DISTURBING FACTORS

Other factors that might disturb a record of the cardiac forces must now be listed. Some of

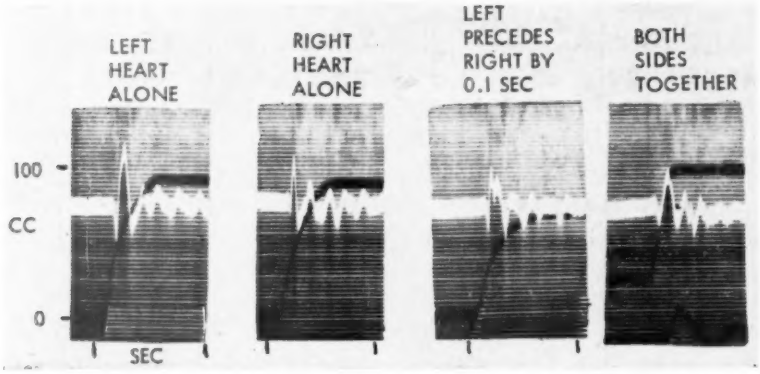

Fig. 2. Relative effects of the right and left heart on the ballistocardiogram. Experiments made in cadavers by injecting into the aorta and pulmonary artery, separately and together. White line = ballistocardiogram; black line = the "cardiac ejection" curve. Note the the ballistocardiogram of the "left heart" (simulated by an injection into the aorta) is much larger than that caused by a very similar ejection from the "right heart" (simulated by an injection into the pulmonary artery). When the two ejections are simultaneous a smooth ballistocardiogram results; when they are asynchronous the conspicuous abnormality is a notched J wave.

these I have not experimented on myself, and I will give my present opinion in the form of answers to pertinent questions often asked me, questions which are undoubtedly in the minds of many doctors.

Do Parts of the Body Move Relative to One Another?: Clinicians accustomed to feel the abdominal organs move with respiration realize at once that the body is not a solid block, although for theoretic purposes it is convenient for the physicists to assume that it is. The problem whether distortion of the record could result from secondary movements of various parts within the body has just begun to receive attention. If there is distortion from this cause, records from ultra-low frequency instruments and from shin bars would be far more subject to it than would high-frequency records, because the much smaller movement of the body frame in space when a high-frequency table is used, would less excite the springs binding the various parts of the body together.

A method of securing information about the binding of the heart to the body was proposed by Von Wittern,[13] and the method could be used on other organs as well. Von Wittern simply determined the change of position of the heart as the force of gravity was applied to it when the subject changed from the horizontal to the upright position. The weight of the heart being known, the character of the binding can be calculated approximately. Burger *et al.*[14] calculate that the elasticity of the heart's binding will have little or no effect on records secured by ultra-low frequency ballistocardiographs. We need data of this kind for other bindings in the body.

Does the Position of the Heart Make a Difference?: One cannot deny that great differences in the position of the heart might make some difference to the record, but in all probability the effect is negligible under most circumstances. The theoretic studies indicate that only a small part of the ballistocardiogram is due to movement of blood while in the heart; by far the larger part is due to forces from blood moving in the vessels. The vessels in the trunk are fixed in position and those in the limbs placed in a standard position at each test. Also, the expulsion tracts of the right and left hearts are at an angle with one another. The normal pendular movements of the heart with respiration bring one tract toward alignment with the vertical—in which we record the forces—while the other tract is rotating away from that line.

Theoretically, I should expect that extreme deviations of the heart from the normal position would result in some diminution of the I wave. I have a record which was secured on a patient the apex of whose heart, after the surgical re-

moval of the left lung, was in the left axilla. This record does show an I wave smaller than normal, and this is doubtless due to the extremely abnormal position. Nevertheless it seems obvious that the normal differences in the cardiac axes of different people and the movement of this axis during respiration can make no important difference in the relation of the ballistocardiogram to the forces which originate it.

Do Differences in Body Build Affect the Record?: Tanner[15] was unable to demonstrate that differences of body type, in Sheldon's classification, could be correlated with any differences in the ballistocardiograms of healthy young men.

Tannenbaum, Vesell and Schack[16] gave their subjects a push and studied the frequency and damping of the subsequent movements of a shin-bar relative to a fixed surface on which the subjects lay. The values found differed considerably in different subjects. Damping increased with age and frequency was more rapid in underweight, less rapid in overweight subjects. They point out that such differences might cause appreciable errors in the ballistocardiogram, which is certainly true for records secured from shin-bars, in which it is this movement between body and table which is recorded. But this conclusion does not hold for tabie records, either high-frequency or ultra-low frequency, for in these methods movement between the body and the table is absent or greatly reduced.

By means of the cadaver experiments, in which the energy of the simulated systole was known, we sought a final answer to questions of this kind. Our cadavers varied from obese to thin, and the frequency and damping of the high-frequency table with the bodies on it was tested for each. But aside from the small improvement which resulted when differences in body surface area were taken into account, we found no evidence that differences of body build produced an error in records taken by the high-frequency instrument in use at that time.

Why Are There No Ballistic Waves Attributed to Cardiac Filling?: This is a very reasonable question. Since the heart must receive, in diastole, as much blood as it ejects during systole, why is it that we ignore, or fail to record, forces developed during the filling of the heart in diastole? The answer lies chiefly in the distensibility of the walls of the great veins and the low pressure within them. Although the flow in the veins equals that in the arteries it is much more steady, so acceleration and deceleration are much less than in the arteries. Also, because the veins are easily stretched the waves initiated by cardiac activity are not transmitted rapidly or far, so they involve little mass of accelerating blood at each instant. With both acceleration and mass much reduced it is not surprising that the normal venous forces are far smaller than the arterial. Indeed it appears that they can usually be neglected.

However, as the venous pressure rises and the venous reservoir becomes tense the forces generated in the venous blood by cardiac activity are sure to be larger than they are in healthy persons. To find no feature of the normal ballistocardiogram which is dependent on movement in the veins does not imply that venous forces may not manifest themselves in certain abnormal conditions, as when venous pressure is raised. I have records in several cases with elevated venous pressure which show large deflections occurring later in diastole than the terminal complexes usually manifest themselves, and I do not hesitate to attribute these to venous forces.

Should Movement of the Heart Muscle Itself Be Considered?: There are several good reasons for expecting that the normal movement of the heart's wall would have little or no effect on the record. First, any object free to move in space when it changes its shape, will not change the position of its center of gravity. Though not completely free to move, the heart is certainly far from fixed. Second, the normal heart wall resembles a hollow sphere and as it expels its contents the movement of each point is toward a common center, and so the forces developed by each moving point would be largely neutralized by those developed by the opposite movements of the corresponding points on the other side of the sphere. Third, surgeons after exposing the pericardium in the course of operations on the heart have commented to me on how very little movement is to be seen before the pericardium is opened. Certainly the position in the body of the heart's center of mass is steadied by the fact

that the auricles fill while the ventricles empty and vice versa.

For theoretic reasons such as these most students of the subject, especially those with training in physics, have been content to regard the ballistocardiogram as caused by the movement of blood and to consider the contributions of the movements of the heart walls as negligible.

But certain of my clinical friends have demurred. To them it is "the heart banging around in there" which causes the ballistocardiogram, and the apex beat is the consequence and symbol of its "banging around," the tangible evidence that force is being delivered to the body which has nothing to do with the movement of blood. Most of these friends see the point if I call attention once more to the situation illustrated by a man inside a little room on wheels; by pushing against one wall he can make it bulge (the apex beat) but this does not move the room in space (the ballistocardiogram) because he is able to push on the wall with his hands only by pushing equally in the opposite direction with his feet. One cannot raise oneself by pulling on one's bootstraps.

However, the "banging around" conception was supported by animal experiments performed by Cossio *et al.*[17] who aimed to rule out the effect of movement of blood on the ballistocardiogram by ligating the great veins and so securing a record while the heart was still beating but presumably not pumping blood. They found that the amplitude of their record under these circumstances might be larger than that found before venous ligation, so they concluded that the movement of blood was but a minor factor in the genesis of the ballistocardiogram, which they believed to be largely due to movement of the heart itself.

However, a careful study of their paper suggests that their technic was so deficient that no such conclusion need be drawn. They applied Dock's method to the shins of dogs and so must have had a more or less flexible connection between recorder and the source of the force. Very few of the curves illustrated resemble either human ballistocardiograms or those now secured in dogs by good technics. Indeed Cossio *et al.* speak of the ballistocardiograms of normal dogs as "pleomorphic," and so I conclude that they had not solved the problem of getting consistent records.

However, Thomas *et al.*,[18] using technics superior to those of Cossio *et al.*, applied the Dock technic to the dog's head and got results very similar to those of Cossio; they also reported increases in ballistic amplitude after interruption of the great veins.

These experiments were repeated by Honig *et al.*[19] with still further improved instruments and a technic that meets all modern standards. Also, these investigators curarized their animals to prevent interfering muscular movements which are so likely to appear in agonal experiments of this type. The results and conclusions were quite different from those of Cossio and of Thomas. In these experiments ligation of the great veins regularly caused a diminution of the I-J amplitude, but some amplitude persisted.

Certainly Cossio's bold experiment has stimulated a lot of work so it seems appropriate to discuss briefly the underlying design. We desire to know the relative contribution of movement of blood and movement of heart muscle to the ballistocardiogram under the conditions in which one takes such records in the clinic. One knows the total of both contributions; that is defined by the control ballistocardiogram. One desires to take away the movement of blood and to leave the movement of the heart unchanged, which would permit one to determine the contribution of the latter from the record secured after venous ligation, and that of the former by the difference between experimental and control records.

Great difficulties exist in such a design even in a simple inanimate system. Consider a compressed spring arranged to move a weight, as in A in Figure 3. On releasing the spring, forces are liberated which can be estimated from the mass and acceleration of the moving parts. Part of the forces are inherent in the movement of the weight, and part inherent in the movement of the spring itself. We desire to separate these two items, so it is proposed to remove the weight and allow the released spring to rise alone, as in B in Figure 3. But obviously the forces developed when the spring moves without its load (as in B, Fig. 3) are not those inherent in the spring when it moves under the weight (as in A, Fig. 3); but

many times larger. This is because the spring, when restrained by the weight, accelerates itself far less rapidly than when it is free of this restraint. One would expect the heart to do the same.

Cossio's and Thomas' experiments on the heart also have physiologic difficulties inherent in them. Ligation of the great veins certainly does not interrupt all filling of the heart; collateral circulation permits some blood to find its way around the ligatures; blood would also enter the heart from the coronary sinus, the thebesian veins and by the pulmonary veins. Thomas *et al.*[18] always found blood in the heart at necropsy after venous ligation.

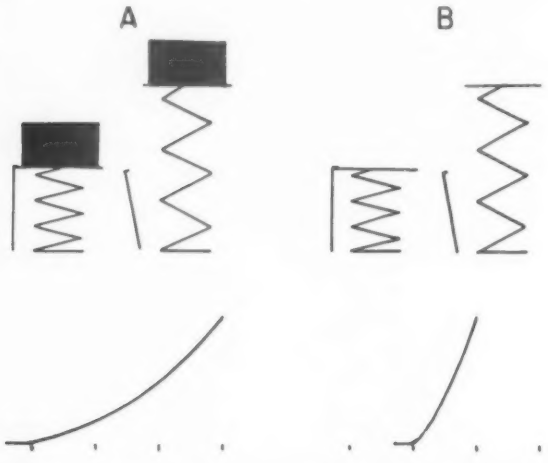

Fig. 3. Difficulties inherent in the design of Cossio's experiment as illustrated by an inanimate system. Effect of releasing a spring: A, with a load upon it; B, without the load. The time curve of the expanding spring is shown below.

When exposed to a killing stress, such as in these experiments, the heart often has a brief period of violent "agonal" beating before it collapses, and I presume that the large ballistocardiograms shown after these cardiac experiments were taken during such an agonal period. Certainly one has no right to assume that the contribution of the movement of the heart's wall under such circumstances gives a true indication of its contribution when the heart is beating normally.

Also, all of us are trained to think in terms of flow and find it more difficult to think of the forces. Thus ligating the aorta, as in Thomas' experiment,[18] effectively stops the flow, but it might well increase the forces developed because the headward movement of blood would be stopped abruptly when thrown against the ligature, rather than gradually when rounding the aortic arch. Leaking back into the ventricle through valves rendered incompetent by the distention of the aorta proximal to the ligature, this blood could be violently thrown out again at each systole even though no venous blood entered the heart. Also forces might well pass the ligature, in the manner so well illustrated by the row of billiard balls in contact; the cue ball strikes one end, and the ball at the other end moves off, the force being transmitted through the column of balls without moving them appreciably.

Such thoughts have led me to doubt whether the problem of the contribution of the movement of the heart wall to the ballistocardiogram can be solved by acute animal experiments designed to deprive the heart of its blood while it continued to beat; there are too many uncertainties. Certainly in excellence of design these experiments are not to be compared with the simple and straightforward experiment of replacing the heart with a pump designed to make no contribution to the ballistocardiogram by its own movement and injecting in a known manner into the great vessels. This has been done many times in this laboratory and, more recently, in a model of the circulation, by Klensch.[8] The results are perfectly clear-cut; the ballistocardiogram as we know it (with the exception of the H wave) is easily reproduced by this means. The H wave seems largely of auricular origin in normal hearts, so the weight of the evidence certainly suggests that movement of the heart wall is not an important factor in the genesis of ballistocardiograms, and it seems proper to neglect it at present.

ORIGIN OF THE WAVES

Having been driven to the conclusion that the force ballistocardiogram gives a reasonably true account of the resultant of the forces originated by the heart, and so can properly be used by clinicians to assess its strength or weakness, we are now in a position to discuss the origin of the individual waves of the force ballistocardiogram

and of the abnormalities of form which are so often seen in the clinic.

Experimental Production of the Normal Ballistocardiogram: This can be reproduced in cadavers by any synchronous injection into aorta and pulmonary artery which accelerates rapidly at the onset of injection, and the waves can be explained as follows.

At the time of onset of the I wave, footward-directed forces from the reaction to the headward movement of blood are unopposed, but they are soon opposed by headward forces, first from the arrest of the headward movement of blood at the aortic arch and in the curve of the pulmonary artery, and then from the recoil to the footward acceleration of blood rounding the aortic arch and entering the thoracic aorta. These headward forces bring the I wave to an end and produce the J wave. The K wave of the older records secured on healthy young persons has proved to be largely an instrumental artifact but that of elderly persons is not, and it seems due to deceleration of blood in the long column in thoracic and abdominal aorta and in the vessels of the legs. The origin of the waves of the terminal group (L, M, and N) will be described by Noordergraaf and Heynekamp in this seminar (p. 748).

The presystolic G and H waves have not been produced experimentally. They undoubtedly have more than one origin. Forces due to the movement of blood caused by auricular contraction provide a satisfactory explanation for much that we see, but not for all, as normal-appearing H waves are not infrequently seen in auricular fibrillation. Mitral or tricuspid regurgitation may be the cause of many of these. Other possibilities have also been suggested, such as abnormal movement of blood within the ventricle itself in the pre-ejection phase of cardiac contraction, as when the rising pressure causes a weak spot in the ventricular wall to bulge outward.

Experimental Production of Abnormalities: In the cadaver experiments we learned to reproduce practically all the forms of ballistocardiographic abnormality seen in the clinic except those involving the H wave. Records of abnormally large amplitude are produced by applying large forces, abnormally small records by applying unusually small forces to drive the injection into the great vessels.

In the clinic one encounters an almost infinite variety of abnormalities of contour and we have certainly not reproduced all of these experimentally. But we have reproduced the main types and the remainder appear to be various combinations of these. Typical abnormal ballistocardiograms secured in the clinic and their reproductions secured experimentally in cadavers are shown in Figure 4.

Thus the very common abnormal type showing absence of the I wave with a persisting J wave is reproduced in the cadaver experiments by any injection with a very slow initial acceleration. A still slower onset of injection causes almost no initial complex at all, or one in which both I and J are minimal, as in Figure 4. Such records indicate weakness of the cardiac contraction. Waves of the terminal complex, L, M, and N, appearing early in diastole, exceed those in systole in size when the injection accelerates slowly but decelerates rapidly (Fig. 4). This is another sign of weakness of contraction.

A split J wave is reproduced by starting to inject the pulmonary artery before or after the start of the aortic injection (Fig. 2), or vice versa. Such records indicate asynchronism of the forces from the two sides of the heart, and this might be due either to intrinsic weakness of one side or to abnormal factors such as high blood pressure which oppose the ejection of blood by one side, without sufficient increase in the strength of the cardiac contraction to overcome the handicap.

The greatest variety of bizarre complexes can be produced by injections which are not smooth, but accelerate and decelerate more than once. One such example is reproduced in Figure 4. Our records contain many other examples, so abnormal and so different one from another that brief description is impossible. Such records reflect incoordination of the ventricular contraction.

The various forms of abnormal ballistocardiograms seen in the clinic which have not been reproduced experimentally are easily explained as combinations of the forms which have been reproduced. It seems that we have a firm grip on the physiologic interpretation of abnormalities.

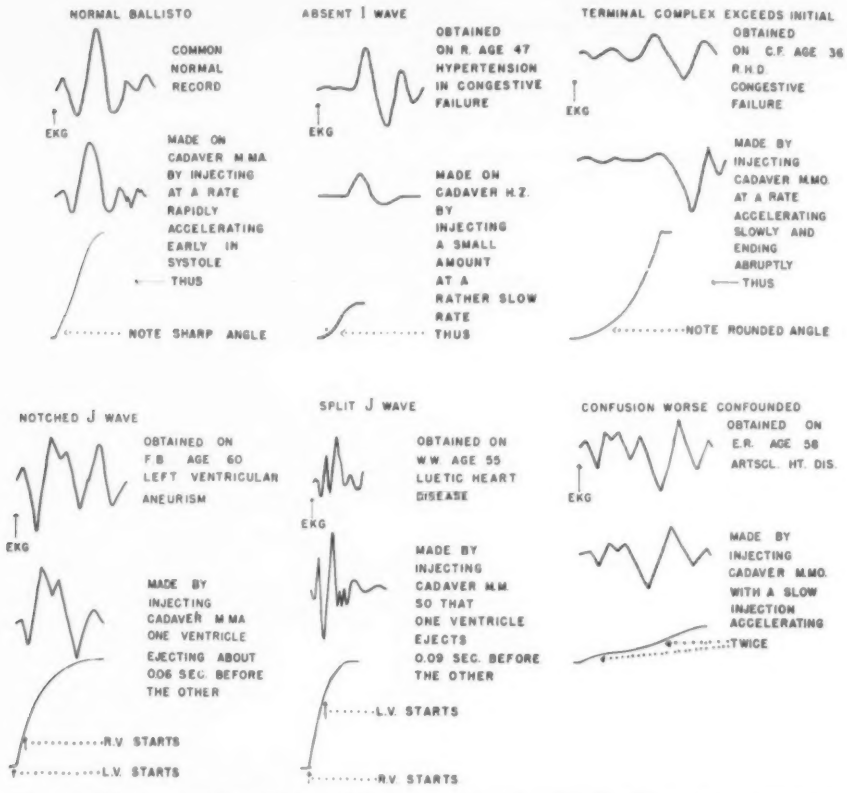
NORMAL BALLISTO
COMMON NORMAL RECORD
EKG
MADE ON CADAVER M.MA. BY INJECTING AT A RATE RAPIDLY ACCELERATING EARLY IN SYSTOLE
THUS
NOTE SHARP ANGLE
ABSENT I WAVE
OBTAINED ON R. AGE 47 HYPERTENSION IN CONGESTIVE FAILURE
EKG
MADE ON CADAVER H.Z. BY INJECTING A SMALL AMOUNT AT A RATHER SLOW RATE
THUS
TERMINAL COMPLEX EXCEEDS INITIAL
OBTAINED ON C.F. AGE 36 R.H.D. CONGESTIVE FAILURE
EKG
MADE BY INJECTING CADAVER M.MO. AT A RATE ACCELERATING SLOWLY AND ENDING ABRUPTLY
THUS
NOTE ROUNDED ANGLE
NOTCHED J WAVE
OBTAINED ON F.B. AGE 60 LEFT VENTRICULAR ANEURISM
EKG
MADE BY INJECTING CADAVER M.MA. ONE VENTRICLE EJECTING ABOUT 006 SEC. BEFORE THE OTHER
R.V. STARTS
L.V. STARTS
SPLIT J WAVE
OBTAINED ON W.W. AGE 55 LUETIC HEART DISEASE
EKG
MADE BY INJECTING CADAVER M.M. SO THAT ONE VENTRICLE EJECTS 0.09 SEC. BEFORE THE OTHER
L.V. STARTS
R.V. STARTS
CONFUSION WORSE CONFOUNDED
OBTAINED ON E.R. AGE 58 ARTSCL. HT. DIS.
EKG
MADE BY INJECTING CADAVER M.MO. WITH A SLOW INJECTION ACCELERATING
TWICE

Fig. 4. How normal ballistocardiograms and the common types of abnormality seen in the clinic can be reproduced in cadaver experiments. There are six illustrations in this figure. At the top of each a ballistocardiogram secured in the clinic and chosen to illustrate the common types of abnormality of form, has been reproduced. Immediately below is a very similar ballistocardiogram obtained in a cadaver experiment by the type of "cardiac ejection" shown below it. Note that it is the manner in which the heart ejects its blood that determines normality or abnormality of the form of the ballistocardiogram.

Summary

From the foregoing account one can see that determined efforts have been made to identify sources of error in the force ballistocardiogram as a record of the resultant of the forces generated by the heart. In few other clinical methods has there been such an extensive hunt. Certainly nothing of much moment has turned up, although we found reason to believe that differences in vessel elasticity and in size of subject would have some effect on the relation between the record and the forces which originate it. An effect of the position of the heart and of arteriosclerosis would manifest itself only if the deviation from the normal was extreme. While various other uncertainties certainly exist, it seems unlikely that they are important.

Clinicians are often forced to use methods which are not perfect and much trouble can be avoided by proper care in the preparation and use of normal standards. In the case of the ballistocardiogram the scatter of the normal population will be due not only to differences in the forcefulness of the hearts of healthy persons, but also to all the other factors which might have some effect on the proper recording of such forces, such as: differences in body size, body habitus, blood pressure, arteriosclerosis and the usual technical errors. But if we identify as abnormal only those outside the statistical limits of normality of such a healthy group, the odds are strongly in favor of a valid identification of abnormality of the cardiac forces.

Using the data from the cadaver experiments as a test, one finds we can identify the magnitude

of the acceleration of the blood with an accuracy about equal to that of the common clinical method of taking blood pressure. It is true that the Riva-Rocci method has greater errors inherent in it than most doctors realize; the point I wish to make is that despite such errors, much important clinical information has been secured by means of it, and its introduction into clinical medicine was responsible for a great advance.

I am hopeful, therefore, that the time has come when doctors will no longer be content to regard heart diseases from the purely anatomic viewpoint, and when a statement of the strength and coordination of the heart's contraction will be considered an essential part of the record of every cardiac case. The ballistocardiogram provides a method of readily securing information on this point without causing the least discomfort to the patient.

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Genesis of Displacement of the Human Longitudinal Ballistocardiogram from the Changing Blood Distribution*

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SINCE THE discovery of ballistocardiography about eighty years ago, it has been clear that events related to the heart's mechanical action were responsible for the body's movement.[1] During the development of this field of research it gradually became clear which physical quantities concerning the internal events are measured with the various current types of ballistocardiographs.[2,3] It has generally been recognized nowadays that the ultra-low frequency ballistocardiograph is a suitable instrument to provide data on three related aspects of the over-all circulatory effects, namely, the displacement, velocity (speed) and acceleration of the internal periodical motion of the center of gravity caused by the action of the heart. These quantities are secured from the ultra-low frequency system by recording its displacement, velocity and acceleration, respectively.[2–5]

The quantitative relationship between the events occurring inside the body and the recorded curves is an old problem. The earliest quantitative investigation concerning the relationship between the internal occurrences and the human acceleration (force) tracing was carried out by Starr and Rawson in 1941[6] applying Machella's data. A similar method of prediction of the force trace was later used by Hamilton and co-workers[7] applying their data secured from previous calculations.

This paper will deal with the prediction of all three aspects of the movement of the human center of gravity [displacement, velocity and acceleration (force)] by means of a new and different approach to the problem.

METHOD OF APPROACH AND RESULTS

Events taking place within the circulation change the distribution of the mass within the body with each beat of the heart. In the first place the right and left ventricles eject their stroke volumes into the corresponding arteries during systole, which is only a fraction of one heart cycle, while the run-off from the arterial to the venous beds goes on during the complete heart cycle; thus the quantity of blood in the systemic and pulmonary beds changes continuously with regard to time. Besides this the quantity of blood in the auricles and in the central veins also changes periodically. Moreover, the movement of the heart, of the large vessels and of the soft tissue in which they are embedded may contribute to a changing mass distribution inside the body. The total change in mass distribution may obviously be described as the movement of the center of gravity within the body,[8] and the result of this movement may be recorded in terms of the displacement, velocity or acceleration of the body itself.

In this paper we shall focus our attention on the effect originated by the changing blood content of the ventricles and of the larger arteries in both the arterial trees. When the right and left heart start to eject their stroke volumes into the

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corresponding arteries, the blood flowing into the root of these vessels causes the blood pressure to increase rapidly and the arteries to distend, first at their orifices. The pressure rise and distention thus created run along the arteries in the distal direction; wherever the pressure (pulse) wave appears, the lumen of the vessel increases, while it decreases as soon as the pressure wave passes by. Thus during the cardiac cycle the distribution of mass in the body is altered, first by the changing volume in the ventricles and then by the wave of changing volume progressing down the arteries. The relation between the flow in the arteries, and the familiar pressure wave (the pulse) is, however, not a simple one. In general there is a time (phase) difference between them.[9]

From these considerations it may be concluded that the movement of the center of gravity (the ballistocardiogram) can be estimated from the flow patterns within the circulation. This method of approach, however, requires not only knowledge of the flow patterns at the aortic and pulmonary valves, but also of flow patterns throughout the circulation. Moreover, the relation between flow and pressure (distention) must also be known. A simpler way of approach follows from the same considerations. The degree of distension of the arteries is related to the pressure curves found in the various arteries, and since the latter is well known, the former can be determined if one has knowledge of the elasticity. This short-cut method does not require knowledge concerning the ejection curve of the heart and the flow curves in the arteries.

Method Based on Ventricular Ejection Curves: The first method was, as the original attempt, applied by Starr and Rawson in 1941.[6] These authors used the ejection curve as recorded by Machella[10] (in dogs) and derived acceleration and deceleration of the blood from this curve mathematically. They divided the aorta and the pulmonary artery into small segments. The masses contained by these segments were multiplied by the values of the acceleration and deceleration of the blood. Alignment according to the pulse wave velocity and summation of the results provided an estimate of the contributions of the aorta and pulmonary artery. Addition of the ventricular effect gave an estimate of the acceleration (force) ballistocardiogram. The authors concluded that the ballistic curve is mainly due to ventricular and aortic effects, while the pulmonary contribution turned out to be a very minor one.

Hamilton *et al.*,[7] who objected to Starr's application of Machella's results, used a similar method of prediction of the force ballistocardiogram, but applied ejection curves estimated from previous calculations.[11] Hamilton and co-workers also concluded that the force ballistocardiogram must be mainly attributed to ventricular and aortic occurrences.

Since these investigations more evidence has been produced suggesting strongly that the ballistocardiographic tracings are mainly due to ventricular and arterial events (Starr's cadaver experiments,[12] Burger,[8,13] Elsbach,[4] Dock[14]), though there is not yet complete agreement (Cossio,[15] and Thomas,[16] dog experiments).

Because of this conflict of evidence we have attempted to predict the three aspects of the internal movement of the center of gravity by applying the above-mentioned second method of approach, which has the advantage that the well-known pressure tracings can be used for the various portions of the arterial trees, the elasticity of which can also be estimated. An extensive description of our method of calculation has been given previously[3,17,18] and only the line of thought will be related here.

Method Based on Pressure and Filling of Various Arteries: The larger arteries (down to an internal radius of 1.1 mm) of both arterial trees, summed up in Table I, were subdivided into small segments. The mass of blood above the end-diastolic level—the excess mass—in each of these was calculated as a function of time with intervals of 20 milliseconds. Multiplication of the excess masses with the appropriate distances to a reference plane passed arbitrarily through the center of both ventricles, and summation of the results, gives an estimate of the expected displacement of the center of gravity as far as this is caused by the events inside the ventricles and the larger arteries. The result is shown as the heavy line in Figure 1, marked D-BCG, instant zero being taken as the instant of opening of the

TABLE I

The Arteries in Which the Changing Blood Content is Taken into Consideration. If the Artery Is Paired Both Are Used

I	VI
Aorta ascendens	A. brachialis
Arcus aortae	A. ulnaris
II	A. radialis
Aorta thoracalis	A. interossea volaris
Aorta abdominalis	VII
III	A. coelica
A. iliaca communis	A. gastrica sinistra
A. iliaca externa	A. lienalis
A. profundis femoris	A. hepatica
A. femoralis	A. renalis
A. poplitea	A. mesenterica sup.
IV	A. mesenterica inf.
A. tibialis posterior	VIII
A. tibialis anterior	A. carotis communis sin.
V	A. carotis communis dex.
A. anonyma	A. vertebralis
A. subclavia	IX
A. axillaris	A. pulmonalis
	Ramus sinister (A. pulm.)
	Ramus dexter (A. pulm.)

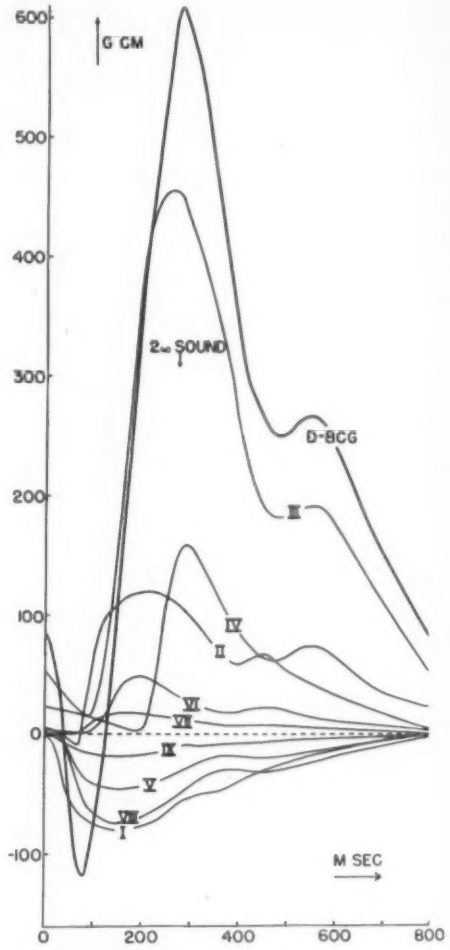


Fig. 1. The predicted longitudinal displacement ballistocardiogram is the heavy line (D-BCG). It is the sum of the contributions of various anatomic portions represented by lighter lines. They are marked by Roman numerals which are identified in Table I.

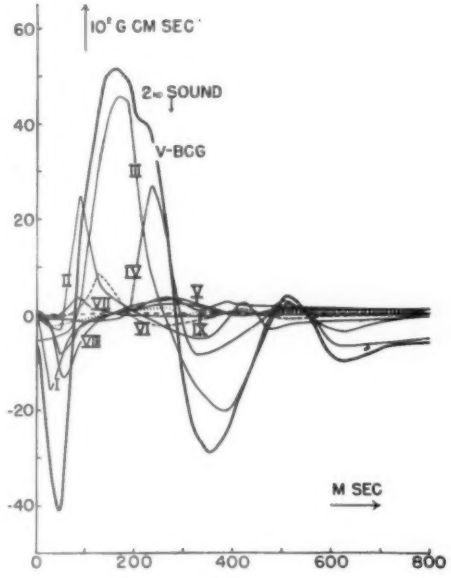
semilunar valves. The contributions of the various portions of the arterial trees are shown by lighter lines in the same figure. The heavy line is a plot of the sum of the lighter ones.

The other two aspects, velocity and acceleration of the center of gravity, depicted in Figures 2 and 3, have been secured from the data plotted in Figure 1, by differentiating once and twice respectively. The vertical scales of the predicted curves in Figures 1 to 3 should be divided by the total mass of subject and ballistocardiograph to find the amplitude of the predicted displacement, velocity, and acceleration curves. This has been done for displacement, velocity, and acceleration by taking a mass of 75 kg, which is a reasonable average total mass for a healthy person plus an ultra-low frequency ballistocardiograph. The composite plot is given in Figure 4 together with average experimental traces of healthy persons.[19] The amplitudes of the predicted curves are in good agreement with the experimental results.[3,13,20–22]

Not only the peak-to-peak values but also the general shape of the predicted and experimental curves are essentially the same. The analogy holds for the relationships with other phenomena related to the action of the heart as for instance the heart sounds (Fig. 4; see Rappaport[23] for another composite sketch of experimental tracings).

In our method of prediction of the human ballistocardiogram only the contribution of the ventricles and of the larger arteries of both arterial trees were taken into consideration and the great similarity between theoretical and experimental results, which emerged, led us to the conclusion that the normal ballistocardiogram must be attributed mainly to these circulatory events.

By calculating the volume changes in the



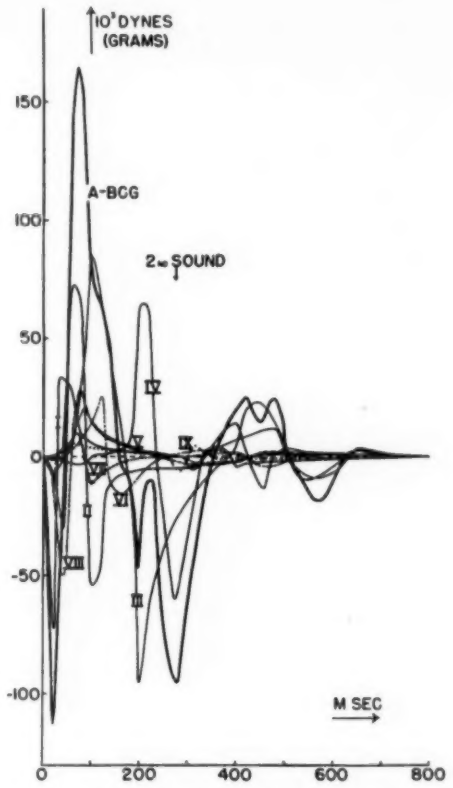


Fig. 2 (left). The predicted longitudinal velocity ballistocardiogram (V-BCG). The lighter lines show the contributions of the various anatomic portions. Fig. 3 (right). The predicted longitudinal acceleration (force) ballistocardiogram (A-BCG). It is the sum of the contributions of the various parts of the arterial trees plotted as light lines.

larger arteries the excess masses present in the limbs at any time can be estimated, and so the plethysmograms of the larger extremities and the trunk can easily be predicted. This calculation was carried out for the forearm and the calf and the results were compared with plethysmograms which have been recorded. This has been discussed in detail elsewhere.[24,25] Our results show a good quantitative agreement between theoretic and experimental curves, and this provides us with an independent check on the validity of our method.

Our conclusion that the normal ballistocardiogram is mainly due to ventricular and arterial effects has also been reached by Klensch and Eger from model experiments in which they proved to be able to produce normally looking arterial pressure and ballistic curves[26,27] by injecting into tubes which simulated the anatomy and elasticity of the blood vessels.

The most striking difference between the experimental and theoretical curves (Fig. 4) is that there is no H wave in the predicted acceleration (force) curve. The H wave is also absent in ballistocardiograms secured in Starr's cadaver experiments in which he replaced the heart by a pump. Indeed, in records secured in living persons, the H wave precedes ventricular ejection and so cannot be due to ventricular systole.

Explanation of Ballistic Movements: It seems worthwhile to discuss the results plotted as the light lines in Figures 1 to 3 a little more closely. It should be noticed first that circulatory effects occurring headward or footward with respect to the reference plane passed through the ventricles by causing a movement of the body's center of gravity, cause the body to move in the opposite direction. Therefore in Figure 5 and in Table II the arteries are distinguished as "headward" and "footward" vessels.

Contribution of a Single Arterial Segment: Let

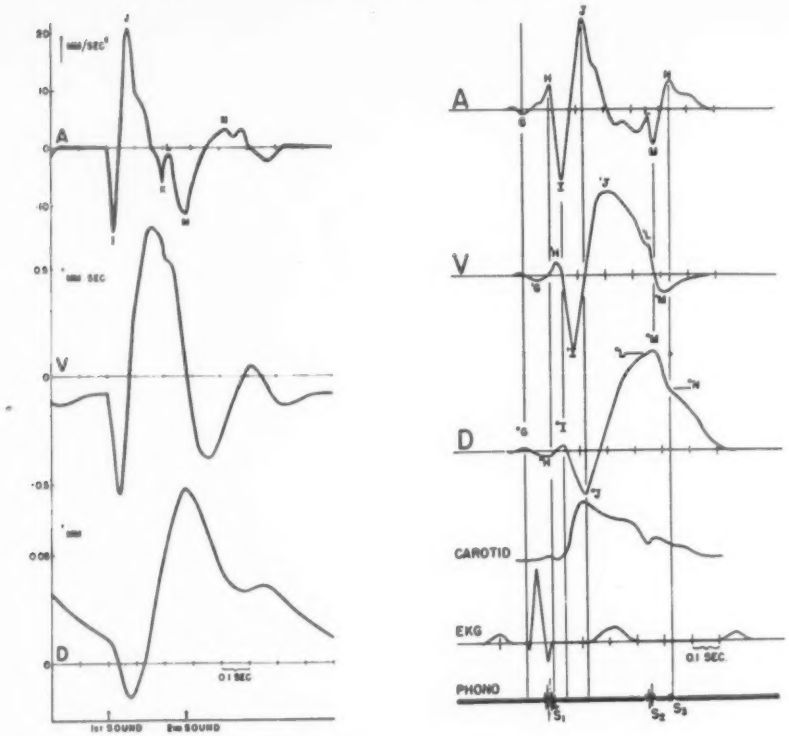


Fig. 4. The right-hand side is a reproduction of average normal acceleration (force, A), velocity (V) and displacement (D) ballistocardiograms secured from an ultra-low frequency ballistocardiograph and published in the Report of the Committee on BCG Terminology by Scarborough and Talbot (*Circulation* 14: 435, 1956; used by permission of the authors and of *Circulation*). The left-hand side pictures the predicted curves taken from Figures 1 to 3 (heavy lines) for reason of comparison.

us now consider the contribution of an arbitrary segment of artery, which is assumed to be so short that the same blood pressure governs throughout its length. A pressure curve, used for an artery with an internal radius of 3.4 mm, is drawn in Figure 5 (top), and is assumed to hold for this segment. This pressure curve gives also the time course of the quantity of blood above the end-diastolic levels. The middle curve depicts the rate (speed) of filling at each instant (first derivative of the top curve). The bottom curve depicts the rate of the change in filling (second derivative of top curve), which indicates acceleration and deceleration in quantity of blood above the end-diastolic level.

Opposite to the curves in Figure 5, the ballistocardiographic effect is indicated. The direction in which the *internal* center of gravity moves is given for "headward" and "footward" segments separately, the *body's* movement being in the opposite direction of the internal effect. When there is a quantity of blood above the diastolic level in a "headward" segment it contributes to a headward displacement of the center of gravity within the body (and the footward displacement of the body to keep its center of gravity unchanged in space). If the amount of blood above the diastolic level is increasing in a "headward" segment of artery (rate of filling positive, middle curve, 2–4; 6–8) then the velocity of the internal center of gravity is in the headward direction. It is in footward direction when the amount of blood above the diastolic level is decreasing (rate of filling negative; 1–2; 4–6; 8–10). The opposite holds for a "footward" segment. When the rate of change in filling is positive (bottom curve, 1–3; 5–7; 9–10) the internal force acts in a headward direction for a "headward" segment. In case

TABLE II

The Arrows Denote the Direction in Which the Mentioned Phenomena Affect the Movement of the Body Regarding Its Displacement, Velocity, and Acceleration. A Downward Pointing Arrow Thus Indicates Footward Effect, and Upward Pointing Arrow Headward Effect

	Displacement tracing	Velocity tracing	Acceleration tracing
"Headward" vessels	Quantity of blood above the diastolic level ↓	Increasing quantity above diastolic level ↓ Decreasing quantity above diastolic level ↑	Rate of change in filling positive ↓ Rate of change in filling negative ↑
"Footward" vessels	Quantity of blood above the diastolic level ↑	Increasing quantity above diastolic level ↑ Decreasing quantity above diastolic level ↓	Rate of change in filling positive ↑ Rate of change in filling negative ↓

the rate of the change in filling is negative (3–5; 7–9), the internal force acts in a footward direction. Again the opposite holds for "footward" segments.

Contribution of Various Portions of Arterial Tree: After this discussion of the contribution of a single segment, the contributions of the various portions of the arterial trees may be looked at a little more closely. The contributions of these portions have been plotted separately in Figures 1 to 3, positive being headward movement of the body. Table II, summarizing Figure 5, may prove helpful in reading these plots. The arrows in Table II denote the direction in which the events in that portion contribute to the *body's* movement. The light lines in Figures 1 and 2 can be easily interpreted making use of Figure 5 and Table II. We shall discuss only the acceleration curves a little further because of the fact that they receive most attention nowadays (Figs. 3 and 4). The downstroke from the base line to the I peak is apparently mostly due to the immediate result of the heart's ejection of blood into the root of the aorta (positive rate of change in filling; Figure 3, I) as was concluded by Starr[22] and Hamilton.[7]

The most important contributions to constitute the I-J upstroke are initially the decrease in the rate of change in filling of the ascending aorta and of the arch (Fig. 3, I) and later the fact that the rate of change in filling of the thoracic and abdominal aorta is positive (Fig. 3, II). The decrease in the rate of change in filling of the thoracic and abdominal aorta and its increase in the iliacs and in the arteries of the upper parts of the legs are the most striking contributions to the first part of the J-K down stroke (Fig. 3, II, III), though the contributions of the other portions are of importance here. The latter part of the J-K downstroke turns out to be mainly caused by the rapidly decreasing rate of change in filling of the iliacs and the arteries of the upper parts of the legs (Fig. 3, III)

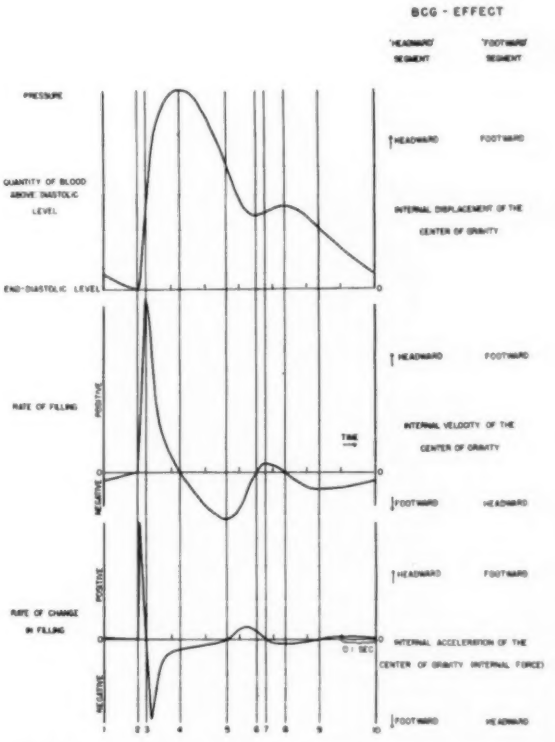


Fig. 5. Evaluation of the ballistocardiographic effects originated in a single segment of artery.

a conclusion also reached by Honig and Tenney.[29] Superposition of the negative rate of change in filling of the last mentioned portion and the positive rate of change in filling of the arteries in the lower parts of the legs (Fig. 3, IV) causes the K-L upstroke. Somewhat later the rate of change in filling of the arteries of the lower legs has turned negative. Superposition of this part of IV and the corresponding part of III causes for the greater part the M peak. For the remaining part of the curve a number of this type of events occurring in different portions are responsible.

This explanation is supported by a recent publication of Reeves and co-workers[28] in which they emphasize the time relationship between the peaks in the second time derivative of the carotid pressure tracing and those in the acceleration record of an ultra-low frequency system. They do not, however, take into account the fact that events in the different parts of the arterial system occur at different instants because of pulse propagation time.

Relation of Amplitude to Rate of Ejection: Starr has shown experimentally[32] that the amplitude of both the initial and terminal complexes depends on the time course of the ejection of blood. If the outflow is abrupt initially, the initial complex shows a large amplitude, whereas the amplitude is small when the initial outflow is gradual. This means that a great acceleration of the blood produces large amplitudes of the force tracing. This is also true for the terminal complexes. An abrupt ending of ejection causes large amplitudes; a gradual stop small ones (Fig. 6). These qualitative observations, that the time course of ejection both at the onset and at the end of ejection are of great importance, are in excellent agreement with our above-mentioned conclusions (compare Fig. 3). Starr's findings have been recently confirmed in model and cadaver experiments carried out by Honig and Tenney.[29] Moreover, the latter authors add the observation that late diastolic vibrations were absent only in those patients without audible evidence of aortic valve closure, which seems to give another confirmation of our theory.

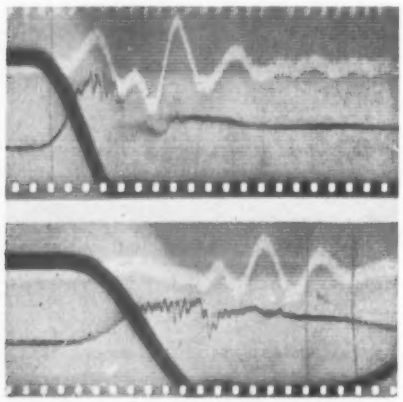


Fig. 6. An example of two simulated systoles in the same cadaver. The injected volume (heavy black line), the central aortic pressure (tiny black line) are recorded simultaneously with the ballistocardiographic force tracing (white line). The latter is recorded from an old type high-frequency ballistocardiograph. Note that the amplitude of the ballistic waves change when the time course of injection changes. (Courtesy of Dr. Isaac Starr).

Discussion

One would expect that if the ballistocardiogram is, for the greater part, based on the circulatory events in the ventricles and in the larger arteries, as is concluded in this paper, the ballistocardiographic phenomena would disappear after occlusion of the vessels immediately around the heart. Cossio[15] and later Thomas[16] and co-workers performed this experiment and observed that, though the pattern changed beyond recognition, the amplitude of the force tracing increased, thus suggesting that other than the above-mentioned circulatory events cause the ballistocardiogram. The most obvious interpretation was then that the heart's movement initiated the recorded tracings. On the other hand, Starr recorded normal traces, except for the lack of an H wave, while he simulated systole at necropsy by injecting into the aorta and pulmonary artery, although the heart was not beating. It was not until very recently that Cossio's experiments have been repeated with improved technics. Honig *et al.*[30] and Scarborough[31] secured the abolition of most of the ballistocardiogram in stopping the circulation while the heart kept beating. These experiments and Starr's critical review of the older dog experiments presented in a previous section of this seminar, seem likely to resolve the old controversy.

The results of the modern dog experiments, of

Klensch's model experiments, and of our quantitative prediction, make it seem very unlikely that the movement of the heart, venous flow, and atrial contraction contribute significantly to the ballistocardiogram, except in the earliest part of systole (H peak in the force trace), a statement which is supported by clinical observations and experiments in dogs (Dock,[14] Honig[30]).

As has been noted above, Starr *et al.* concluded both from their calculations[6] and from results secured in experiments in which they simulated systoles in cadavers,[32] that the contribution to the ballistocardiogram of the movement of blood in the pulmonary circulation is a minor one. To these findings Dock[33] objected that the pulmonary contribution had to be many times bigger than the systemic one in order to explain the respiratory variation in the amplitude and pattern of the ballistocardiogram seen in normal persons. The conception that the movement of blood in the pulmonary circulation makes only a minor contribution to the ballistocardiogram, is strongly supported by our calculation. It may be objected that lack of published information about the physical properties of the pulmonary circulation forced us to assume that these properties were similar to those of the systemic circulation. Because of this assumption, our estimation of events in the pulmonary circulation contains an element of doubt which does not apply to those made on the systemic circulation. Further investigations will be necessary to elucidate this point.

Conclusions

Displacement, velocity and acceleration of the internal center of gravity in the normal human body predicted from physiologic and anatomic data are presented. The predicted curves are essentially equal to the well-known results secured experimentally. It is concluded that the ballistocardiogram must be attributed mainly to the circulatory events occurring in the ventricles and in the larger arteries. The contributions of the various portions of the arterial trees, as estimated from the calculations, are displayed separately. Thus the physiologic events responsible for each part of the ballistocardiogram can be described quantitatively.

The results are critically compared with those obtained from investigations done by others.

Acknowledgments

The authors wish to thank Dr. Isaac Starr for his continuous interest and Miss Ann Hearl for her contribution in the calculations.

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Report on Therapy

Infection Complicating Peripheral Arterial Occlusive Disease

Treatment with Intraarterial Histamine and Antibiotics*

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UNCONTROLLED infection is the most frequent cause for amputation of a limb whose arterial blood supply is reduced. Preservation of such an extremity should depend on prompt and adequate enhancement of collateral blood flow and concentration within the infected area of antibiotics at bactericidal levels. Seventy-three patients who had this problem were so treated by methods already described. Their responses to treatment have been recorded and correlated with the etiology of the occlusion, location of infection, weight bearing during treatment, diabetes, and venous edema so that their influences on the results could be evaluated. Recent literature has been annotated to contrast the mechanisms and results of our and other forms of current therapy to serve as the basis for a rational choice of treatment.

PATIENT MATERIAL

There were 65 patients whose obliterative disease was caused by arteriosclerosis and secondary thrombosis. Forty-three patients were diabetic. There were also eight patients with thromboangiitis obliterans due to their smoking cigarettes.

Without exception all patients had had one or several forms of treatment elsewhere or in our our clinics, given in random order. Amputation above or below the knee had been recommended for some. The peripheral vascular status of each patient was carefully evaluated. The location of major arterial blocks was determined by the absence of pulsating arteries and decrease in the readings on the oscillometer and at times by arteriograms. The status of the collateral arteries and the adequacy of arterial blood flow was judged by observing the distribution and intensity of changes in color and temperature of the skin which developed during and after the arterial infusion of a dilute solution of histamine.[35,36]

The adequacy of the venous circulation was judged not by the amount of peripheral edema but by the rate of its disappearance while in bed and reappearance when up. The infection of each patient was evaluated by cultures when the lesion was open. The infecting organisms were tested for their sensitivity to antibiotics. Collateral diseases which could influence the fate of the infection, when present, were evaluated. These included arterial insufficiency, edema, local fibrosis and necrosis, pressure sores, reflex vasospasm from pain and fear, ischemic neuropathy, and local trauma from irritating medication.

PLAN OF TREATMENT

Treatment was carried out in each case according to the following plan:

(I) Insufficiency of blood flow
  (a) Augmentation of arterial flow

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(1) Vasodilating therapy: repeated arterial infusions of histamine
(2) Reflex vasospasm: relieve pain by sedation, nerve blocks, and allay fears
(3) Increase of hydrostatic pressure by lowering of leg not more than 15° below heart level when no edema is present
(4) Reduce metabolic needs of tissues by resting the limb

(b) Augmentation of venous flow
(1) Reduce venous pressure—horizontal position of leg
(2) Reduce edema
a. Increase renal clearance of sodium and water with diuretic's especially if cardiac failure is present
b. Increase flow via lymphatics with hyaluronidase
(3) Cure phlebitis—no smoking; anticoagulants in acute cases

(II) Infection
(a) Bactericidal and bacteriostatic antibiotics
(1) Repeated arterial infusions of antibiotics suitable for intravenous use
(2) Antibiotics orally, subcutaneously, and locally

(b) Minor surgical care
(1) Immobilization, unroofing corns and calluses, incision and drainage, debridement of necrotic or nonviable tissues

(c) Major surgical and orthopedic care guided by the exact knowledge of local vascularity obtained from an arterial infusion of histamine. Amputations of gangrenous toes, removal of sequestra, open guillotine, transmetatarsal amputation

(d) Failure of treatment—amputation above or below knee

(III) Collateral diseases
(a) Systemic—diabetes, cardiac and renal failure, malnutrition, vitamin deficiencies
(b) Local—skin prophylaxis, dermatoses, neuropathies, static foot imbalances, prosthesis

The arterial infusion had two purposes, one, the evaluation of collaterals as described above and the other, therapy.[32,33] It transported into the affected limb the vasodilator histamine, the bactericidal antibiotics,[45] the enzyme hyaluronidase for the reduction of venous edema,[38] and vitamins for their possible help with tissue repair or wound healing.[26]

TECHNIC OF ARTERIAL INFUSION

Supplies for an arterial infusion included the following: 250–500 cc infusion bottles of normal saline or 5 per cent dextrose in water, 2 hole bottle cap "Venopak" type, a sterilized atomizer bulb with valve removed for pumping air into the infusion bottle and continuous flow syringe "Kaufman B-D" type. Drugs used in the infusion bottle included histamine acid phosphate supplied in 1 cc ampules or 5 cc vials, nontoxic antibiotics suitable for intravenous use and hyaluronidase vials of 1500 t.r.u.

Histamine: The amount of histamine phosphate varied with local and systemic conditions. The starting dose was 1.25 mg in 300 cc of diluent and this low dosage was maintained if the distribution and intensity of the erythema was adequate. When a history of effort angina or bronchospasm was obtained the starting dosage was reduced to 0.5 mg. If the erythema after an infusion was inadequate the amount of histamine was increased to the maximum levels of 2.75 mg. in 300 cc and 4.5 in 500 cc. If the foot remained mottled during an infusion the concentration of histamine was reduced by increasing the amount of diluent. The infusions were given daily when the infection was severe, spreading, and painful. When less threatening three treatments a week were given. Patients with a history and symptoms of peptic ulcer received 60 cc of aluminum hydroxide gel before and during each infusion.

The ability to introduce the arterial needle into an easily palpable artery or one barely or completely nonpulsatile can be mastered by practice. The needles used were short beveled 20 and 22 gauge, $1^1/_2$ inches long, 20 gauge, 2 inch "baby spinal" needles and rarely 18T, $1^1/_2$ inches and 2 inches in length. The skin was infiltrated with procaine and the needle directed cephalad at an angle determined by the palpating fingers' estimation of the depth of the artery. When the femoral pulsation was absent it was very often possible to find the artery. By keeping in mind that the artery lies between the femoral nerve laterally, irritation of which by the needle causes paresthesias on the anterior surface of the thigh, and the femoral vein lying deeper and medially whose blood on aspiration was not bright red, the lumen of the artery was often entered. Tattooing the skin with carbon black over the point of the first successful entry made the next arterial puncture more simple. Displacement of the needle from the artery during the infusion caused local pain or pain

referred medially down the thigh. On withdrawal of the needle firm pressure over the artery must be maintained for three or four minutes. If pain developed or became more intense in the area of infection during the infusion the peripheral nerve supplying the painful area[47] was blocked before the next infusion. This prevented pain and reflex vasospasm.

If acute thrombophlebitis was present, the anticoagulants, heparin and dicoumarol, were prescribed with the usual precautions. The phlebitis of thromboangiitis required no anticoagulants, subsiding three weeks after the cessation of the use of cigarettes. When chronic postphlebitic edema was present 500 t.r.u. of hyaluronidase was added to the infusion bottle.

Antibiotics: Antibiotics chosen on the basis of cultures of the wound and sensitivity tests were added to the infusion bottle in maximal dosage. They never caused local pain or thrombosis of the artery. However, if the block was located above the femoral artery and femoral blood pressure was low, to prevent possible irritation 500 cc of diluent was used to carry the antibiotic. These were also given orally and subcutaneously. Antibiotics in wet dressings, ointments, and powders often cause pain, maceration, and allergic reactions and were therefore seldom used. Fungus infections were treated locally with mild soap solutions, gentian violet, and the undecylinic acids.

Surgical Procedures: The choice and scope of minor and major surgical procedures when local conditions demanded intervention depended on a knowledge of the collateral blood supply which became manifest after several histamine infusions. Continuing arterial infusions often made it possible for the surgeon to successfully perform and heal an open type amputation through the metatarsals when without their help, below the knee amputations would have been unavoidable. When necrosis and infection spread in spite of treatment amputation below the knee was advised.

During treatment attention was paid to the patient's nutrition, hemogram, and intake of protein and vitamins.[17,20] In order to accelerate healing 500 mg of vitamin C and 1,000 μg of B_{12} were at times added to the infusion bottle when the infection was controlled.

Results

In Table I are listed the outcome of treatment and significant clinical data of each patient. Factors other than those listed undoubtedly influenced the response but did not lend themselves to tabulation for purposes of comparison. Some of these were depth and accessibility of infection, amount and location of necrotic tissue, degree of insufficiency of collateral arterial and venous circulation, type and virulence of the organisms, and traumatization of viable tissues by adjacent structures, by patient's self treatment or by physicians' prescriptions.

The 73 patients were divided for analysis into two main groups based on the etiology of their occlusive disease. Arteriosclerosis was the cause in the larger group consisting of 65 patients, while thromboangiitis obliterans was the cause in the remainder. Of the patients with arteriosclerosis, 54 (83 per cent) were cured and 11 (17 per cent) were not helped. Diabetes was present in 35 of these patients. The incidence of success was the same for the diabetic and the nondiabetic.

To study the interdependence between results of treatment and clinical data the 65 patients with arteriosclerosis were analyzed as to the location of infection, the presence of edema and phlebitis, and the effect of hyaluronidase and of ambulation. The locations of their infections fell into two groups, one, the toes and the other, the rest of the foot and leg. Our multidisciplinary regimen was successful in 94 per cent of the patients with infections of one or more toes. When the infection involved the foot or the leg, the incidence of success fell to 71 per cent. Edema could be expected to influence the results of treatment. When edema was the result of venous incompetency the incidence of failure rose to 30 per cent from the over-all rate of 17 per cent. When caused by phlebitis and periphlebitis it rose still higher to 38 per cent. Some patients received hyaluronidase in their arterial infusions. A single infusion containing hyaluronidase repeatedly caused a striking reduction for two or three days in the amount of fluid discharging from an ulceration of the foot or leg. Repeated infusions maintained this reduction in edema and with bed rest lowered the high incidence of failure. Statis-

TABLE I
Clinical Data in 73 Patients Treated with Intraarterial Histamine

Case Number	Etiology	Oscillometric readings of leg		Status before treatment					Antibiotics and hyaluronidase	Response to treatment			
		Upper Half	Lower Half	Infection			Edema and cause	Organism cultured		Surgical therapy	Infection	Healing	Weight bearing
				Skin	Bone	Gangrene							
1	AS	0.5	0	Toe	Toe	Toe	—	Staphylococcus A	E S	Debrided self-amputation	Cured	Yes	Yes
2	ASD	1.5	0	Toe	—	—	P+	Staph A, Yeast	Ta Pe	Nail removed	Cured	Yes	Yes
3	AS	0	—	Toe	Toe	Toe	—	Staph A	Ta	Self-amputation	Cured	Yes	No
4	AS	0.5	—	2 Toes	Toe	—	—	Staph A	E	Enzyme powder	Cured	Yes	No
5	AS	1.5	1.0	4 Toes	Toes	2 Toes	P+	Nonhemolytic Streptococcus, Staph	Pe E C	Debrided	Two cleared	Yes	Yes
6	ASD	0	—	Toe	—	Ulcer	Ca+	Staph and B. Coli	Ta T	Debrided	Cured	Yes	Yes
7	ASD	0	—	3 Toes	Toe	Ulcers	—	Staph and Coli	Ta T	Enzyme powder	Cured	Yes	Yes
8	AS	0.2	—	Toe	Toe	—	—	Staph and N H Strep	S	Incised	Cured	Yes	Yes
9	AS	0.5	—	Toe	Toe	—	—	Staph and Proteus	Ta	—	Cured	Yes	Yes
10	ASD	1.0	—	Toe	Toe	Ulcer	—	Staph	Ta	—	Cured	Yes	No
11	ASD	0.7	0.5	Toe	Toe	—	Ca+	Staph	E	Drained	Cured	No	Yes
12	ASD	0	—	Toe	Toe	Ulcer	—	Staph	S	Debrided	Cured	Yes	Yes
13	ASD	0	—	Toe	—	Ulcer	P+	Staph	S	Callus debrided	Cured	Yes	Yes
14	ASD	0.5	0	Toe	—	—	P+	Staph	S	Callus debrided	Cured	Yes	Yes
15	ASD	0.5	0.5	Toe	Toe	Ulcer	—	Staph	E	—	Cured	Yes	Yes
16	AS	0	—	Toe	Toe	Ulcer	—	Pyocyaneus	A	Sequestra removed	Cured	Yes	Yes
17	AS	0.5	—	Toe	Toe	—	—	Staph	E	Debrided	Cured	Yes	Yes
18	AS	0	—	Toe	—	—	—	Staph	E	—	Cured	Yes	Yes
19	ASD	0	—	Toe	—	Toe	—	Staph	E	—	Cured	Yes	Yes
20	ASD	0.1	—	Toe	—	Toe	—	Coli	A	Debrided	Cured	Yes	Yes
21	ASD	0	—	Toe	Toe	—	Ca+	Staph	A	Amputated	No	No	No
22	ASD	0	—	Toe	Toe	—	—	Staph	A	Nail removed	Cured	Yes	Yes
23	AS	0	—	Toe	Toe	Toe	—	Strep Viridans, Coli	Pe	Osteotomy	Cured	Yes	Yes
24	ASD	0.5	—	Toe	Toe	Toe	—	Staph	Pe	Self demarcation	Cured	Yes	No
25	ASD	0.5	—	Toes (3)	Toes	Toes	—	Staph	Pe A	Bone removed	Cured	Yes	No
26	AS	0	—	Toes (3)	—	—	—	Staph	A	Debrided	Cured	Yes	Yes
27	ASD	0.5	—	Toe	Toe	Toe	—	Coli	Pe A	Demarcation	Cured	Yes	Yes
28	AS	0	—	Toes	Toe	Toe	—	Hem Strep	Pe A	Demarcation	Cured	Yes	Yes
29	ASD	1.0	0.5	Toes	Toe	—	—	Staph	Pe A	—	Cured	Yes	Yes
30	ASD	2.5	2.0	Foot	—	Ulcer	—	Coli	A	—	Cured	Yes	No
31	ASD	2.0	—	Heel and leg	—	Foot	—	Coli and Pyocy	Pe A	Leg amputated	No	No	No
32	AS	1.0	0.5	Toe and foot	Foot	Toes (2)	—	Enterococcus	Pe A	Leg amputated	No	No	No
33	ASD	3.0	1.0	Toe and foot	Foot	Toes (4)	—	Entero and Pyocy	Pe A	Transmetatarsal guillotine	Cured	Yes	No
34	ASD	0	—	Foot and ankle	—	—	—	Staph and Coli	Pe A	Died	No	No	No
35	ASD	0	—	Toe and foot	—	—	—	Staph	A	Debrided	Cured	Yes	No
36	AS	1.0	—	Heel	—	—	—	Staph	Pe	Core removed	Cured	Yes	Yes
37	ASD	0.5	—	Toes and foot	Foot	Toes	—	Coli and Pyocy	A	Debrided tendon severed	Cured	Yes	Yes

38	ASD	0	—	Ankle	Metatarsal	—	—	Strep Vir, Coli	A	—	No	None	
39	AS	0	—	Leg	Tibia	Ulcer	PP++	Coli, Pyocy	Pe A	Debrided	Cured	Yes	No
40	ASD	1.0	—	Leg	Tibia	Ulcer	PP+	Staph	A	—	Cured	Incomplete	Yes
41	ASD	1.0	—	Leg	Tibia	Ulcer	PP+	Staph	A	—	Cured	Complete	No
42	AS	0	—	Foot and ankle	—	—	P++	Coli	A	—	Cured	Healed	No
43	AS	0	—	Foot	—	—	P++++	Coli	A	—	No	None	Yes
44	AS	1.5	—	Leg	Tibia	Ulcer	P+++	Staph	A	—	No	None	Yes
45	ASD	0	—	Leg	Tibia	Ulcer	PP++++	Staph, Alkaligenes	Ta E Hy	Enzyme powder	Cleared	None	Yes
46	ASD	0	—	Leg	—	Ulcers	V+++	Staph	Ta E	—	Cleared	Slow	Yes
47	ASD	0.5	—	Leg	—	Ulcers	V++	Staph	Ta	—	Cleared	Yes	Yes
48	ASD	0	—	Leg	—	Ulcer	V+++	Staph	Ta	—	Cleared	Yes	Yes
49	ASD	1.5	—	Leg	—	Abscess	VV+	Staph	Ta Hy	—	Cleared	Yes	No
50	AS	0	—	Leg	—	Ulcer	PP+++	Staph and Pyocy	Ta Hy	—	No	No	Yes
51	AS	0	—	Leg	—	Ulcer	PP+	Staph	Ta Hy	—	Cleared	Yes	No
52	AS	0.5	—	Heel	—	Ulcer	—	Staph	E S	Callus removed debrided	Cleared	Slow	No
53	ASD	0.5	—	Foot	—	Sinus	—	Staph	E	Debrided metatarsal pad	Cleared	Slow	No
54	ASD	0	—	Foot	—	Sinus	P++	Staph and Proteus	Ta	Callus removed	Cleared	Slow	Yes
55	ASD	0.5	—	Ankle	—	—	—	Staph	E	Incised	Cleared	Yes	No
56	AS	0	—	Dorsum foot 8 x 3 cm	—	Tarsal	—	Staph	Ta E	Previous skin graft failed	Cleared	Yes	Yes
57	ASD	0	—	3 x 3 cm dorsum	—	—	—	Staph	E	New thrombosis caused gangrene	No	No	Yes
58	ASD	0	—	Toes and foot	4 Metatarsals	Toes and foot	—	Staph and Coli	Ta Pe	Transmetatarsal guillotine	Cleared	Yes	No
59	ASD	1.0	—	Toe and foot	Metatarsal	Sinus	—	Staph	Ta	Trimmed callus	Cleared	Yes	No
60	ASD	0	—	Toe	Toe joint	Sinus	—	Staph	Ta	—	Cleared	Yes	No
61	ASD	0	—	Foot	Metatarsal	Sinus	Ca+	Staph	Ta	Callus trimmed	Cleared	Yes	No
62	ASD	0	—	Toe and heel	—	—	—	Hem Strep	E	Debrided	Cleared	Yes	No
63	ASD	0	—	Dorsum foot	—	—	—	Staph and Coli	Ta	Debrided	Cleared	Yes	No
64	ASD	0.1	—	Leg	—	—	—	Staph	Ta	—	Cleared	Yes	No
65	TAO	0	—	Toes and foot	Toes	Ulcers	PP++	Hem Strep and Pyocy	Ta E Hy	Much self-treatment	No	No	Yes
66	TAO	2.0	—	Toe	Toe	—	P+	Hem Staph	E Hy	Self-amputation	Cleared	Yes	No
67	TAO	0.5	—	Toes	Toe	Ulcers	P+	Staph	Ta Hy	—	Cleared	Yes	Yes
68	TAO	0	—	Leg	—	Ulcer	PP+++	Staph	S Hy	Phlebectomy failed to help	Cleared	Almost complete	Yes
69	TAO	0	—	Toes	Toes	—	P ++	Staph	Ta	—	Cleared	Complete	Yes
70	TAO	0	—	Toe and foot	—	Toes	PP++	Staph	Ta	Amputation	No	No	No
71	TAO	—	—	Upper tibia	Tibia	Open wound	—	Strep	Ta	Revision of stump	Cleared	Yes	No
72	TAO	1.0	0.7	Toe and leg	Toe	—	P+	Staph	Ta	—	Cleared	Yes	Yes
73	ASD	0	—	Toe	Toe	Ulcer	Ca++	Staph and Coli	Ta T	Debrided	No	No	Yes

Abbreviations: Etiology
- AS Arteriosclerosis
- ASD Arteriosclerosis with diabetes
- TAO Thromboangiitis obliterans

Causes of edema
- V Varicose veins
- P Phlebitis
- PP Periphlebitis
- Ca Cardiac Failure

Grade of edema + to ++++

Antibiotics
- Pe Crystalline penicillin G
- A Chlortetracycline HCl
- Te Oxytetracycline HCl
- Ta Tetracycline HCl
- E Erythromycin
- C Chloramphenicol
- S Streptomycin
- Hy Hyaluronidase

tically, ambulation and nonambulation caused little difference in the final results of treatment. However, persistent edema and infection of the plantar tissue necessitated nonambulation.

There were only eight patients in the second group with thromboangiitis obliterans. All had phlebitis due to smoking or infection or both. Since the number of cases was too small to analyze, only the response to treatment was recorded. Of the six patients cured by treatment, two had infection of the toes, three of the foot, and one had an ulcerated infected open stump of the upper third of the tibia. Four were ambulatory and two were on crutches during treatment. Treatment was of no avail for two patients who had severe periphlebitis, ulcerations, and extensive edema of the foot and leg, and both had amputations.

Causes of Failure of Treatment: The basis for failure of treatment in the 13 patients of both groups could be divided into several categories. First was the lack of collaterals available for vasodilation. This became apparent when the erythema of histamine failed to reach below the knee after the first infusion and to spread to the ankle by the sixth infusion. Second was an uncritical acceptance for treatment of patients whose infection and necrosis were so extensive that treatment was destined to fail even if their circulation had been normal. Third was a combination of severe arterial and chronic venous insufficiency complicated by periphlebitis, fibrosis, ulceration, and secondary lymphangiitis. Fourth was the inability or unwillingness of some patients to cooperate with the long regimen of treatment.

Discussion

Bross[9] stated that when a comparative evaluation of therapy was to be carried out he preferred statistics based on a study of variations within a patient, i.e. responses of the same patient to different therapies given in random order. Based on this thesis the 85 per cent overall incidence of success in the group of 73 patients treated previously without success by a variety of other methods of treatments given in random order would support the superiority of the arterial infusion of histamine as the treatment most likely to succeed. This must be due to an increase in blood flow rather than the direct delivery of antibiotics.[24] When infection continues its spread into poorly vascularized areas to choose treatment on a trial and error basis invites trouble. Therefore, by annotating the literature, we will contrast the relative capabilities of our and other current forms of treatment. This may serve as a basis for the immediate choice of therapy.

Comparison of Forms of Treatment

There are two approaches to therapy: enhancement of collateral circulation and removal or circumvention of the arterial occlusion.

Sympathectomy: Sympathectomy hopes to prevent vasoconstrictor stimuli from reaching arteries and to cause permanent vasodilatation. The variability in location and distribution of the sympathetics and coexistence of accessory and transposed trunks[1,22] are a frequent cause of failure. Even a sympathectomy from D_2 to S_2 could not guarantee complete denervation of the lower extremity. If vasodilatation did occur it quickly diminished because an increased reactivity developed in the arteries denervated. This is Cannon's "law of denervation" which Grant[20] believed was due to an increase of up to one thousand times in the sensitivity of the arterial wall to adrenalin, since acetylcholine, its antagonist, had disappeared from the denervated artery. Clinically, Telford[45] noted that after sympathectomy limbs lose their color and warmth in a few days. Barcroft and Swan,[3] by plethysmographic studies, confirmed this reversal. On the sixth day flow was so reduced that it could not reach the level attained after indirect heating before the operation. By the 14th day it was still less. Lynn and Barcroft[28] found that in the patient with obliterative disease, if an increase in blood flow did develop in the foot after sympathectomy it fell almost to the preoperative level within a month. This explains the variability in the results of surgical sympathectomy for intermittent claudication.[3,12,15,23,25,27,31] Allen stated that most patients cannot walk further after sympathectomy since, as Kirklin explained, only the circulation of the skin was increased.[25] Hertzman *et al.*[22] showed that the vasomotor responses were limited to the hands and feet. Lynn[28] also found

the effects limited to the feet and hands and none in the leg after denervation at L_2 and L_3.

Barcroft and Dornhorst[4] explained that sympathectomy affects only the anastamotic arterioles. The nutritional arterioles were not dilated by sympathectomy because unlike the anastamotic arterioles they were unresponsive to adrenalin. This difference in reactivity coincided with findings that nutritional arterioles responded to histamine and the anastamotic to sympathetic block.[35] Shepherd[42] obtained a similar vasodilatation after histamine was infused into the brachial artery. Rappaport *et al.*[41] using radioactive sodium clearances found that sympathectomy did not increase blood flow in the muscles. These differences in reactivity of small arteries may, in part, be the bases for relief of intermittent claudication by arterial histamine in 16 patients after they had not been helped by lumbar sympathectomy.[34] According to Hertzman,[22] immediate relief of pain rarely reported after sympathectomy was due to chance presence of afferent pain fibers among the sympathetic fibers, but this was considered impossible by White.[47]

Antiadrenergic Drugs: Antiadrenergic drugs have been purported to increase peripheral circulation. Tolazoline (Priscoline), an example of this group, has been given orally and subcutaneously and by some intraarterially. Since its degradation was very slow even arterial introduction could not fix the drug within the affected limb and prevent systemic diffusion of the drug, causing nausea, hypotension, convulsions, and cardiac ischemia.[37,40] A solution of histamine infused at a rate of 100 μg/min caused a more extensive and deeper erythema than 50 mg of tolazoline in 2 cc of diluent introduced into the same artery of patients with severe arterial disease.[37] In a study of 250 patients Prandoni and Moser[40] stated that an increase in walking tolerance was not to be expected. In a similar study[37] 17 patients failed to improve, seven received moderate help while seven became so ill that treatment had to be discontinued.

Comparing drugs which produce vasodilation by their direct action on small and large arteries, histamine alone was able to cause maximal dilatation when obliterative disease was present.[35,36] Greenfield *et al.*[21] found that an infusion of acetylcholine into the brachial artery at the rate of 10 mg/min caused a vasodilatation which was less than that of reactive hyperemia. Histamine infused at 75 μg/min caused full dilatation with the hand submerged in cold water.[2] Clinical evidence supporting the efficacy of histamine as a permanent vasodilator has been reported by many workers.[2,5,6,9,14,18,19,29,32–34,42,43] In a total of 233 patients 85 per cent obtained relief of intermittent claudication and rest pain after 6 to 15 infusions of histamine.

Surgical Procedures: Technical surgery through the availability of the homologous arterial graft, the autologous venous graft and synthetic cloths[30] has tried to replace the occluded aortic bifurcation and replace or bypass an obstructed femoral artery. Actual opportunities for such attempts are not commonly available or indicated as analysis of our six-year case load of 243 patients shows. Occlusion in the aorta was found in only 14 instances in this large group. The dim prospects of finding the ideal patient with but one occlusion in the femoral artery are predicted by the careful studies of Dibble[13] on amputated limbs. He found the incidence of but one occlusion to be only 6 per cent, with the highest incidence of a single occlusion in the tibial arteries. In our large series this percentage would have yielded only 14 patients, a figure to be further reduced by the presence of infection, severe venous disease, or visceral disease.

The available operations have two bases for failure, the immediate and the delayed. The immediate and most common cause for failure is thrombosis of the graft variously ascribed to an inadequate arterial outflow in the leg and severe and widespread occlusion in the thigh and leg. The reported incidence of immediate failure has ranged from 73 per cent for end-to-end to 13 per cent for end-to-side anastomosis.[11,12,15,27] Kirklin[25] limits his grafts to the bifurcation of the aorta because of his lack of technical success with the femoral and iliac arteries.

Late failure may follow immediate success. Grafts are destroyed by the antigen-antibody reaction initiated by the presence in the body of the homologous graft and the synthetic cloths,

both foreign bodies,[10,44] a fate similarly shared by other homologous grafts of skin, cornea, and bone. When activated by the foreign tissue or cloths the antibodies caused dehiscence, absorption, and occlusion by thrombosis of the graft.[10] Cloth and autologous venous grafts may be blown out by the high arterial blood pressures.[39]

Arteriectomy peels off the endothelium and the thrombus. LaFontaine limits his attention to occlusions not more than 2 cm in length. Operative reports[15] are mainly pessimistic because the artery becomes thrombosed again.

Comparative Value of Various Methods: In summary, these annotations indicate that the use of homografts and synthetics is experimental, infrequently indicated, technically difficult and its success statistically too uncertain. Permanent improvement is infrequent in the aorta, rare in the thigh, and impossible in the leg. Antigen-antibody reactions destroy the graft and occlude its lumen by thrombosis.[44] Sympathectomy is technically inadequate, its effect being limited to the foot where vasodilatation is transitory and quickly reversed. Tolazoline and similar drugs are mild vasodilators, clinically ineffective, and a menace to visceral function and life. By contrast, histamine, a natural product of the body, has proved itself an effective and often a permanent vasodilator when given by the arterial route. Two hundred forty-three patients treated by seven investigators show an 85 per cent incidence of success in the relief of intermittent claudication and rest pain without morbidity. The literature and experience prove the superiority of arterial histamine. This method should be the primary choice.

ANTIBIOTICS

Effective interaction between the infecting organisms and the antibiotics depended on vascularity being established. Eagle *et al.*[16] stated that the therapeutic activity of a given dosage of penicillin rested on the total length of time it remained at bactericidal levels at the site of the infection and the time required for the organisms to resume self multiplication. Only penicillin could be given by a nonarterial route in sufficiently massive doses to reach any desirable level. For other antibiotics, all more toxic, only their arterial introduction was able to guarantee the highest local concentration. Blum *et al.*[7] found that this gave higher concentrations in the bone marrow than any other route. Comparing serum concentrations in the antecubital and femoral veins after the infusion of antibiotics into the occluded femoral artery showed that the serum concentration in the femoral vein was two or more times that in the antecubital vein. At such high levels a bacteriostatic drug could become bactericidal.[33] Histamine and the antibiotics given together by arterial infusions thus created a clime favorable for minor or major intervention and enabled the patient's own immune mechanisms[46] to control infection and heal tissues.

Conclusions

(1) A multidisciplinary regimen based on the repeated intraarterial infusions of antibiotics and the vasodilator histamine has successfully cured infections in limbs with severe arterial obliterative disease.

(2) Success was found to depend on the availability of collaterals for augmentation by histamine, sensitivity of organisms to antibiotics, and meticulous surgical care.

(3) When the occlusion was due to arteriosclerosis the incidence of success was 85 per cent. The presence of diabetes had no statistical effect on the result. Edema due to severe venous insufficiency sharply increased the incidence of failure but bed rest and the addition of hyaluronidase to the infusions decreased this. Ambulation was harmful both when the infection involved weight bearing surfaces and when peripheral edema was present. The incidence of success in patients with thromboangiitis obliterans was as high as in those with arteriosclerosis and venous insufficiency.

(4) This treatment made extensive local surgery more often possible and successful.

(5) The superiority of this treatment is based on these results and a reconsideration of the current literature.

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Historical Milestones

Descriptions of the Endocardium by Bouillaud (1835) and Bichat (1800)

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IT IS difficult for the modern cardiologist to think back to a time when the endocardium was unknown. This delicate structure, so unobtrusive in the normal, so important in disease, tends to be "taken for granted," and one assumes that, like so many other anatomical structures, it must have been discovered by Vesalius or by one of his followers during the Renaissance. It is therefore astonishing to learn that the classical description of the endocardium and the classical statement of its importance in disease date from the nineteenth century.

Jean-Baptiste Bouillaud (1796–1881), the author of the following description, was an illustrious pupil of illustrious teachers. He had studied with Dupuytren, Corvisart, and Magendie. He was an outstanding clinician, and in the fashion of the day—a fashion which we to our detriment have relinquished—had a wealth of experience in morbid anatomy. While Bouillaud is now remembered chiefly for his important "law of coincidence" between heart disease and rheumatic fever,[1] his description of the endocardium and his recognition of its participation in disease can still be read with pleasure and profit. The following excerpt is translated from his *Traité clinique des maladies du coeur*, Paris, 1835, volume 1, pp. 21 ff.

OF THE ENDOCARDIUM OR INTERNAL MEMBRANE OF THE HEART (BOUILLAUD)

Although it has been somewhat neglected by anatomists, the study of this membrane is of great importance to the physician. I name it the *endocardium* to contrast it with the term pericardium, which refers to the external envelope of the heart. The endocardium is in effect, to the internal surface of the heart what the serous layer previously described is to the external surface.

I have stated that it is of great importance to know well the endocardium or internal membrane of the heart. It is easy to become convinced that this is true if you consider that diseases of this structure are much more common than anyone had realized up to the present time and are perhaps more common than diseases of the pericardium itself. Endocardial diseases almost always go unrecognized in the acute stage and frequently become chronic. I am not exaggerating at all when I say that diseases of the endocardium or internal membrane of the heart are the usual site or origin and the most frequent fundamental or generating cause of the many organic lesions of the valves, walls, or cavities of the heart which formerly—and even nowadays—have been jumbled together under the vague and common name of aneurysm.* But let us return to our subject.

This is the arrangement of the endocardium in the chambers of the left side of the heart. We will start from the root of the aorta. The endocardium is continuous with the internal membrane of the aorta and with that of the coronary arteries. Starting from the aorta the endocardium is reflected around the sigmoid [aortic] valves, enters the left ventricle and invests it

* The term aneurysm formerly included *hypertrophy* and *dilatation*.

completely, passes around the columnae carneae, envelops the tendons of those which insert into the two layers of the mitral valve. In effect it divides to invest both sides of each leaflet. It covers the inner aspect of the left atrium and its appendage, and goes on to join the internal membrane of the pulmonary veins.

In the chambers of the right heart the endocardium has the same arrangement as it has in the left heart. Starting at the root of the pulmonary artery it is reflected around the pulmonic valve, reaches the right ventricle, invests it completely, and passes over the columnae and the tricuspid leaflets just as it does in the left heart. It spreads over the inner aspect of the right atrium and joins the internal membrane of the superior and inferior venae cavae. It is directly continuous with the internal membrane of the coronary veins of the heart, which, as we know, open into the right atrium.

In the normal condition the endocardium is white, semitransparent and pellucid, like serous membranes. It absorbs readily; hence the red color which is often seen in the interior of the heart, in circumstances which I shall attempt to define in a later paragraph.

The thickness of the endocardium does not exceed that of the finest serous membranes, such as the arachnoid, for example. The endocardium is a little thinner in the chambers of the right heart than in those of the left, and is thinner in the ventricles than in the atria. It is noticeably thicker near the arterial and atrioventricular orifices than elsewhere. Moreover in cases in which the endocardium has been chronically inflamed, it is there that we find in the most marked degree the anatomical changes which characterize this disease, among which we must include thickening of the endocardium and of the subjacent cellular and fibrous tissues. The endocardium may become as thick as a fibrous membrane. In such circumstances numerous superimposed layers can often be described in it; the same happens in inflammation of the other serous membranes. It is evident that of these layers it is only the deepest which properly belongs to the endocardium; the others are really nothing more than organized pseudomembranous strata. These false membranes, organized in this way, are usually incomplete and scattered and form whitish and lactescent spots analogous to those which are so often found on the pericardium.

In some cases endocardial thickening does not represent the organization of the false membranes or parasitic layers which we have just described, but, as I have previously stated, is due to hypertrophy of the subjacent layer of cellular tissue. In the normal the endocardium is so intimately adherent to this cellular tissue that it can only be detached in little shreds, especially in the ventricles. In certain diseased states, on the other hand, the endocardium can be separated from the subjacent cellular tissue by a moderately strong pull and it comes off in large strips. We shall give many instances of this in the course of the present work.

About the valves the two layers of endocardium are placed back to back and are so firmly adherent that they cannot be separated. They are to some degree fused with the fibrous component of these valves and can be detached from it only near the base, where they separate to enclose between them the tendinous or fibrous zone which surrounds the orifices of the heart. (Footnote by Bouillaud: At this place the internal and external membranes of the heart are almost in contact with one another through their adherent sides. This proximity is one of the reasons why inflammation of the pericardium is so often accompanied by inflammation of the endocardium, and vice versa.) In consequence of certain pathologic conditions of the valves, the endocardial layers which form part of the valve become thickened and hypertrophic in the way I have previously shown.

In the normal the free surface of the endocardium is perfectly smooth. In consequence of certain morbid affections the membrane may become irregular, wrinkled, and so to speak rugged. This sort of "unpolishing" necessarily increases the friction in the column of blood which passes through the chambers of the heart.

Neither vascular twigs nor nerve filaments are seen in the fine web of the endocardium in normal conditions.

It is not known whether the endocardium, by analogy with the pericardium, secretes a serous fluid for lubricating the internal surface of the

heart. Since this surface is always in contact with the blood, it is therefore always in a state of bland humidity favorable to the movement of the column of blood.

Bichat

It is possible that Bouillaud's ideas about the endocardium were influenced by those of his precursor Marie-François-Xavier Bichat (1771–1802), whose *Traité des membranes* (1800) is one of the foundation-stones of modern anatomy. It is instructive to compare Bouillaud's description with the vitalistic description of Bichat, published 35 years earlier. The following excerpt is taken from a translation of Bichat's *Treatise* prepared by John G. Coffin and published at Boston in 1813 (pp. 138 ff.).

Bichat on the Lining of the Vascular System

We are embarrassed by the same uncertainty when we attempt to class the internal membrane of the vessels. Its nature, yet little known, seems to deprive it of all methodical division.

This is the amount of our anatomical information respecting it.

This membrane, considered in a general manner, and as forming a continued surface in all the vessels which it lines, may be referred to two principal divisions; one corresponding to the black blood and lymph, the other containing the red blood. The first commences in the capillary divisions of the venous and absorbent system, lines their innumerable ramifications, their branches, and their trunks; is continued into both through the opening, into the subclavian veins, and thoracic duct, covers the right auricle and ventricle, the pulmonary artery, and all its divisions. The second has its origin in the commencement of the pulmonary veins, lines them, as well as the left auricle and ventricle, the aorta and its branches, incredibly multiplied.

These two surfaces, without doubt, communicate where the arteries terminate and the veins begin; there is nevertheless a clear line of distinction between them, and they each possess a mode of sensibility, having relation to the kind of blood with which they are in contact.

This manner of considering the internal surface of the vascular system, in showing two distinct portions, one constantly transmitting to the lungs the blood and lymph from all parts of the body, the other returning to every part the blood elaborated in the lungs, leads us to consider this organ as the general termination of the circulation, as being, with all the rest of the body, in a reciprocity of continual action . . . .

The inside of the internal membrane of the vascular system is incessantly moistened with a mucous fluid, the sources of which are still unknown, and which guards it from the impression of the blood, with which it is in contact. We know the numerous valvules, with which this internal membrane is interspersed in the veins and lymphatics.

What is the nature of it? We have no datum respecting it; less extensible than any one of the membranes already described, it breaks by the least effort, as we see in aneurym and in ligatures on the arteries, strongly tied. Its mode of sensibility is hitherto little known.

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Combination of Dextrocardia, Bundle Branch Block, and Myocardial Infarction

Case Report with Vector Analysis of Electrocardiogram

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THIS case is reported to emphasize the value of vector analysis of the routinely recorded electrocardiogram. Its usefulness is exemplified here in the interpretation of a complex abnormal tracing, combining the patterns of dextrocardia, bundle branch block, and acute myocardial infarction in a single cardiogram.

CASE HISTORY

The patient, an 89-year-old white female, was admitted to Good Samaritan Hospital on March 31, 1957 complaining of right upper abdominal pain of several hours' duration. During the week prior to admission she had experienced three episodes of similar pain, each lasting less than one hour. In the interim periods she was apparently without symptoms. The pain was like a "gas-pressure," and no associated sweating or dyspnea was noted. The pain was not referred.

Her significant past history included the knowledge that her heart was "in the right chest." She had a nonfunctioning gall bladder and nonfunctioning left kidney revealed by x-ray examinations in 1953. No definitive therapy for these conditions had been performed. Some five years prior to her present admission she had undergone surgery for a small bowel obstruction caused by adhesions about a ruptured ovarian cyst.

Physical examination at the time of admission revealed: Temperature 98, pulse 90, respirations 26, blood pressure 138/80. The patient was not in acute distress. Examination of the lungs revealed scattered basilar rales and some diminution of breath sounds in both bases. The PMI was in the 6th intercostal space at the right midclavicular line. Heart rate was 90/min and regular; a basilar, grade 3 systolic murmur was heard, loudest in the aortic region; no thrill was felt. The abdomen was moderately distended and the liver questionably palpable one finger's breadth below the left costal margin and nontender. Pulses were palpable throughout and no peripheral edema was present.

Laboratory findings of significance included: PCV 38, hemoglobin 12.0 gm, WBC 7,750 with a normal differential, sedimentation rate 25 mm/hr, prothrombin time 75 per cent of normal. The urinalysis was normal, BUN 14.0, blood sugar 122. Serology was negative. A chest x-ray showed dextrocardia with cardiac enlargement, in-

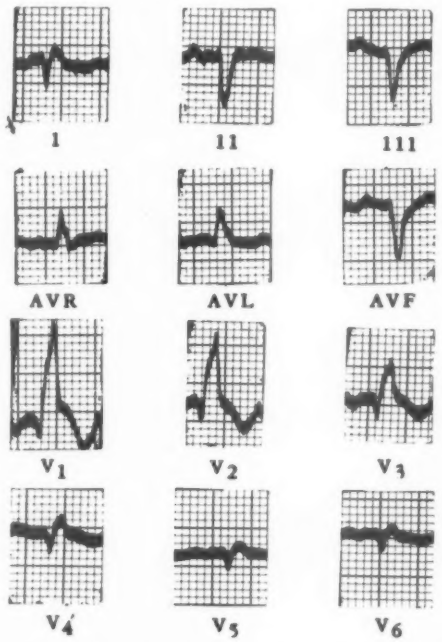

Fig. 1. Electrocardiogram recorded at time of admission to hospital.

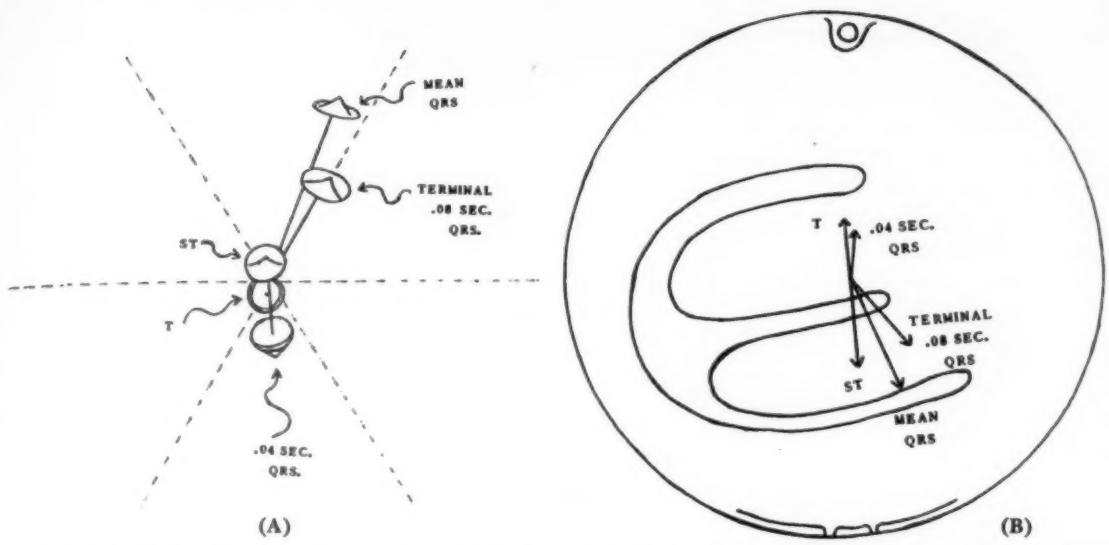

Fig. 2. (A) Frontal plane view of vectors involved in the writing of the electrocardiogram in Figure 1. (B) Same vectors, as viewed in the anterior-posterior plane of the chest.

creased perivascular markings, and minimal bilateral pleural effusion.

Analysis of Electrocardiograms

The electrocardiogram is shown in Figure 1. The analysis of this tracing by plotting of the vectorial forces involved is represented in Figures 2A and B. The following points are of particular interest in the figures, according to criteria outlined by Grant and Estes.[1]

(1) The vector representing the first 0.04 sec of the QRS complex does not point in the same general direction as the mean QRS vector, as one sees in a normal tracing. It is rotated almost 180° in space from the mean (Fig. 2B) and points inferiorly and posteriorly from the sternum.

(2) The T wave vector also points almost directly posteriorly from the sternum (Fig. 2B), forming a large angle with the mean QRS vector. This angle would normally be 60° or less.

(3) The vector of the ST segment is directed distinctly anteriorly (Fig. 2B), pointing at the sternum and nearly perpendicular to the frontal plane. In the normal ECG, and even with dextrocardia and bundle branch block combined, this vector should assume the same general pathway as the T vector.

(4) The vector of the final 0.08 sec of the QRS, as well as the mean QRS vector, point anteriorly, somewhat superiorly, and to the left (Fig. 2A), establishing that the last portion of the ventricles to be depolarized, and, therefore, the area to which the electrical impulse is delayed (blocked) lies in this area of the chest, from an electrical viewpoint.

Comment

The only cardiac abnormalities which would account for this combination of electrical events would be dextrocardia, right bundle branch block, and acute myocardial infarction simultaneously recorded. The ST vector points to the area of anteroseptal myocardial infarction, the T vector and the vector of the first 0.04 sec of the QRS point directly away from it. The terminal QRS vector points to the part of the

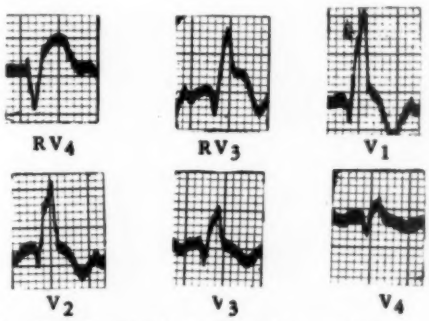

Fig. 3. Supplemental chest leads recorded 12 hours after admission to hospital.

right ventricle farthest from the source of ventricular depolarization (Fig. 2B).

The possibility that this pattern of bundle branch block could actually represent peri-infarction block was considered, but seems eliminated by the direction of the terminal QRS vector toward the right ventricle rather than the infarct. This vector also points well outside of the area to which the terminal vector pointed in peri-infarction block simulating RBBB in the series reported by Dodge and Grant.[2]

Figure 3 shows supplemental ECG leads taken at a later date to substantiate the exact area of infarction.

Summary

(1) A case report is presented which revealed an ECG representing an unusual combination of cardiac abnormalities of dextrocardia, right bundle branch block, and acute anteroseptal myocardial infarction.

(2) The vector analysis of the ECG is shown to emphasize the value of this method of approach in the interpretation of the routinely recorded electrocardiogram.

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Proceedings of the Ballistocardiograph Research Society*

Edited by SIDNEY R. ARBEIT, M.D., F.A.C.C.

Sympatho-Adrenal Function During Nitroglycerin Treatment of Coronary Artery Disease

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Studies have been made of the changes in the ballistocardiogram produced by nitroglycerin in the experimental animal and in the patient during treatment of coronary artery disease. In experimental animals such changes have been correlated with direct measurements of the elicited changes in ventricular contractile force and arterial pressure. These and other studies indicated that ballistocardiography is a useful guide in estimating acute changes in ventricular contractile force and the work load on the heart. An increase in both the work load and ventricular contractile force results in a decrease in the depth of the Ia wave with a corresponding increase in the slope of the Ia-Ja wave. Corresponding changes were observed in the normal subject with infusions of arterenol. Such changes were also observed in patients subject to angina pectoris during intervals of pain and electrocardiographic changes associated with myocardial ischemia. A decrease in the work load on the heart results in an increase in the depth of the Ia wave concomitant with an increase in the amplitude of the ballistocardiogram. Nitroglycerin elicited these changes corresponding with the relief of pain and prior to much improvement in the electrocardiogram.

Such findings would tend to emphasize the importance of the reduction in work load as a factor in the relief of anginal pain. However, further animal studies of the influences of nitroglycerin on the response to epinephrine and arterenol are necessary before a conclusion can be drawn. Preliminary investigations have shown that nitroglycerin produces a sympatho-adrenal reflex increase in myocardial contractility during the interval of elicited hypotension. This type of reflex might also explain the increased vasoconstriction measured during intervals of shock following coronary occlusion.

A New Quantitative Method of Estimating the Initial Acceleration of the Aortic Blood—the Snap of the Cardiac Contraction—from the Ballistocardiograph

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When systole is simulated at necropsy a record is secured of the amount of blood ejected into the aorta at each instant. From this record the initial acceleration of the blood can be readily computed. This is defined as the acceleration occurring in the first 0.08 sec of ejection. This initial acceleration, which may be thought of as defining the "snap" of the cardiac contraction, has been compared with the slope of the H-I segment in 76 simulated systoles secured in 7 subjects, 5 of which were perfused with blood, 2 with water. The relation between the H-I slope and the initial acceleration is striking in every subject, the correlation coefficients being 0.97, 0.96, 0.93, 0.88, 0.92, 0.87, and 0.98 in the 7 subjects. However, the slopes of the regressions differ from subject to subject, a difference depending on the size of the subject. Multiplying the H-I slopes by the subject's body surface area brings the slopes together and the correlation coefficient of the whole data is then 0.86. Indeed the remaining scatter seems altogether to be attributed to the errors inherent in the experiment and measurement of the records.

Measurement of Stroke Volume by the Ballistic Method

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Measurement of cardiac stroke volume has been a major aim in ballistocardiography. In the past the methods of computing stroke volume have been based on formulae which were in one or more respects empirical

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and dependent upon the Fick or Grollman methods for the determination of the necessary constants.

The present work is an attempt to make the computation of stroke volume from the ballistic pattern a direct procedure and independent of calibration by another method.

Equations of motion for the low frequency, critically damped ballistocardiograph which were set up in earlier work were examined and extended. The equations for the special case of the normal heart were applied to data from normal human subjects. The mean deviation of the ballistic results from 46 observations obtained by the Fick method was 18.8%. For 5 normal subjects on whom a total of 14 observations were made under changing conditions of cardiac output the mean deviations from the Fick values of the ballistic results on each subject were much less (ranging from 7 to 17%), showing that a considerable degree of dependability is possessed by the method for the indication of changes in stroke volume.

Extension of the computation to the more general situation of the abnormal heart was presented.

A Further Consideration of the Events Originating the Human Longitudinal Ballistocardiogram

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The availability of new data concerning the distensibility of the main pulmonary arteries created the possibility to improve our previous prediction of the ballistocardiographic effect caused by the pulmonary circulation and resulted in an effect about three times as important as estimated originally although it again appears to be of a far smaller magnitude than the systemic contribution. The experimental data, obtained by other investigators, on which the estimations are based are presented and the method of prediction reviewed briefly.

In the prediction mentioned above only the larger arteries were included. The results of an attempt to estimate the ballistocardiographic effect in the displacement, velocity, and acceleration curve provoked by the change in blood content of the many smaller arteries are discussed. The amplitude of this effect turns out to be roughly around 25 per cent of the total amplitude of the ballistocardiogram.

Finally, a cardiac ejection curve and thus the stroke volume can be estimated from an evaluation of the volume-time relationships of the large and small arteries of the systemic bed. Both results are in fair agreement with the data secured with the aid of well-known methods.

Magnetic Tape Recording of Biologic Data. Advantages and Methods

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The purpose of the present investigation has been to find out how far the methods that have been developed in the telemetering industry for communications with rockets and satellites can be used to advantage in biologic work. The advantages may be expected to be of two sorts, an increase of flexibility of recorded data, making it possible to rework it in different ways so that it may be variously treated at a later date, and in respect to recording data in more than a few channels, there is the chance that there might be financial saving per channel. By use of such technics it may be possible to record on one inexpensive magnetic tape recorder information of up to at least 18 channels. With the purchase of only a four channel graphic oscillograph this information, either in its original form or in reworked form, could be graphically displayed four channels at a time.

The essential feature of the proposed methods of recording is use of magnetic tape. The storing of data in this form means that it remains as good as the original source, alive and reworkable for the future. Examples of what is meant by reworkable is that graphic data stored electrically could later be integrated, differentiated, run faster, run slower; it could be added to or subtracted from, multiplied by or divided by any other graphic function. It could be run through electronic frequency or Fourier analysers, or be squared after such process so as to give the power vs. frequency spectrum.

The simplest solution for such multichannel recording is a multihead magnetic tape recorder. At present, however, these are too expensive for the ordinary laboratory. By using a multiplexing technic developed for telemetering one can do the same thing at a more reasonable cost.

The technic is to carry each channel on a standard Inter Range Instrumentation Group subcarrier oscillator, mix the channels, and record on one channel of ordinary music store high fidelity tape recorder. The demultiplexing is done with fixed frequency discriminators tuned to each of the subcarrier oscillator frequencies.

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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumé of work in progress or recently completed.

Aldosterone Antagonists as Antihypertensive Agents

TWO NEW synthetic compounds were recently reported to antagonize competitively the acute renal excretory actions of desoxycorticosterone acetate (DCA) and aldosterone in laboratory animals by Kagawa, Cella, and Van Arman (*Science* 126: 1015, 1957), and in man by Liddle (*Science* 126: 1016, 1957). The compounds were 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl) propionic acid gamma lactone (*SC-5233*) and its 19-nor derivative (*SC-8109*) (*J. Am. Chem. Soc.* 79: 4808, 1957).

Dr. F. M. Sturtevant (Division of Biological Research, G. D. Searle & Co.) recently examined the ability of *SC-5233* to prevent the induction of hypertension in rats by DCA or adrenal regeneration, at the suggestion of Dr. Kagawa, and also to reduce metacorticoid hypertension. It was found that the compound inhibited the pressor action of DCA and was also hypotensive in metacorticoid rats treated acutely or chronically (*Fed. Proc.* 17: 413, 1958; *Science* 127: 1393, 1958). The hypotensive activity of *SC-5233* was not preferable to its DCA blocking action, however, because metacorticoid rats are no longer under the active metabolic influence of exogenous DCA. Moreover, *SC-8109*, which was more potent in Dr. Kagawa's renal excretory studies, was consistently unable to block the pressor action of DCA. Dr. Sturtevant concluded that the two properties of *SC-5233* were not directly related.

Following the Skelton procedure for inducing adrenal-regeneration hypertension in rats, chronic treatment with *SC-5233* prevented the rise in blood pressure and the cardiac hypertrophy without materially affecting body weight, survival, saline intake, compensatory renal hypertrophy, or adrenal regeneration. Since *SC-5233* had a hypotensive activity of its own, it was impossible to tell whether these results were due to a competitive blockade of the steroids secreted by the regenerating adrenal. It will be of interest to learn of the effects of *SC-8109* on this type of hypertension, an experiment currently being performed by Dr. Clifford I. Chappel.

The Vascular Effects of Stool Straining

The potentially dangerous effects of straining at stool have been known for many years. Recently, Drs. D. Selman, A. Halpern, N. Shaftel, H. G. Birch, S. Samuels, H. Shaftel, and P. Kuhn have attempted to define the cardiovascular and peripheral vascular effects of such straining on a group of normal subjects during defecation, both on the commode and on a bedpan. This group was contrasted with a group of chronically constipated patients. (A preliminary report has appeared in *Angiology* 9: 99, 1958.) The normal group had the lowest average number of straining efforts per bowel movement, and the constipated group the largest number.

Electrocardiographic changes, most often

RS-T segment and T wave alterations, occurred in approximately 19 per cent of experimental Valsalva straining efforts among healthy individuals. In "phase II" of the Valsalva maneuver, it is known that the cardiac output becomes very low and that in "phase IV" there is a marked overshoot of systolic and diastolic blood pressures. It would appear that these phenomena could be dangerous to a patient suffering from coronary artery disease. If so, this is one argument against the use of the bedpan. In the studies mentioned it was shown that a properly selected constipation corrective can normalize the straining effort pattern of the constipated group.

During defecation the frequency of more pronounced increases in venous pressure (exceeding 30 mm Hg), both in the antecubital and saphenous veins, was lowest among the normal subjects on the commode, intermediate when the bedpan was used, and highest among the chronically constipated. In controlled straining at different pressures, the increase in venous pressure varied with the effort exerted, and was similar in the calf and forearm. The rise, however, was more abrupt in the calf.

Both straining at stool and controlled straining markedly affected the segmental (forearm and calf) and digital (finger and toe) blood flow. At the start of the strain, the blood flow dropped sharply and the peripheral resistance rose. As the strain effort continued, vascular resistance tended to decline in parallel with the mean blood pressure, until, after several seconds, there was a modest increase in both these parameters. When the strain was released, there was a sudden drop in peripheral resistance and usually a slight rise in blood flow. This was soon followed by a period of vasoconstriction, the intensity of which was proportional to the straining effort. A variable period of vasodilatation followed this. Then the blood flow and peripheral resistance returned to control values.

Changes in venous pressure, blood flow, and small vessel caliber can cause a loosely attached clot from the veins of the legs or the pelvis to break off and embolize. This is an additional reason for avoiding the straining efforts of defecation, which resemble those of the Valsalva maneuver, especially in those patients in whom pulmonary embolism is likely to occur.

Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D., F.A.C.C.*

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Immediate Indoctrination in Clinical Hypoxia

AT LAST we may come to grips with the problem of how we may give a direct answer to the question, "What are we going to do about hypoxia right now?"

An illuminating occurrence at a New York City obstetrical hospital fired the initial spark in the reply to this question. Several staff conferences had previously been held at this institution on the subject of asphyxia of the newborn; suitable equipment had been purchased by the hospital. On the morning in question, a request was received to anesthetize a patient for a cesarean section. When the apneic, flaccid baby was delivered and passed to the waiting resident physician for resuscitation, it promptly became evident that she was unfamiliar with the technic to be used and with the equipment which was standing by. The anesthetist, an outside physician, who had conducted the staff conferences, was called upon to leave the anesthetized mother and to resuscitate the baby. At the conclusion of the operation he was asked by the surgeon to return later in the week to discuss the death of a mother, which had occurred on the table, in the course of a cesarean operation, apparently the result of aspirated vomitus. These two overlapping incidents kindled the spark which initiated 135 intensive courses in the prevention and treatment of hypoxia, from April 1947, monthly, through April 1958.

At the outset, it was realized that didactic instruction was not enough. This must be integrated with live clinical material and human cadaver instruction. Many logistic complications had to be overcome to provide this material so that it would synchronize with didactic instruction at predetermined dates and hours. Antivivisection resistance must be met, animals must be secured and anesthetized, and a regular supply of cadavers must be arranged,

Between the monthly sessions in New York City, courses were presented in Boston, Philadelphia, Washington, Chicago, Colorado, San Francisco, Honolulu, Los Angeles, and Miami. During the period noted, more than 150 Residents of the Department of Hospitals of New York City, and some 60 exchange students from German universities were instructed without charge, a major task of unsubsidized instruction, relieved only in part by solicited scholarships. Through the years, almost all civilized countries were represented in these groups.

One day, in a talk with Dr. George E. Armstrong, Director of Bellevue Medical Center, Dr. Armstrong remarked "Here is Dr. Beck in Cleveland talking about cardiac resuscitation and here you are talking about respiratory resuscitation. You two should get together." Dr. Armstrong was the catalyst in fusing these separate viewpoints. Dr. Claude Beck became a member of the Board of the National Resuscitation Society. In June 1957, Dr. Robert M. Hosler, who conducted Dr. Beck's course in the prevention and management of cardiac standstill, came to New York City and took the N.R.S. Course in respiratory resuscitation. In September of the same year Dr. Flagg, who had established and carried on the N.R.S. courses, went to

* President, National Resuscitation Society.

Cleveland and took the Beck course. In December, Dr. Beck invited Dr. Flagg to come to Cleveland and present the respiratory portion of the Beck course. In April 1958, the Beck team was invited to come to New York City for the purpose of offering combined instruction. This was presented on April 24–25, 1958 as the first combined course in respiro-cardiac resuscitation.

The Respiratory Factor in Cardiac Resuscitation

The new term "respiro-cardiac" reflected realism in the sequence of treatment. Flagg had been profoundly impressed by the Beck course, for the customary declaration, "The heart has ceased to beat, the patient is dead," was no longer true. The victim whose heart had ceased to beat was not irrevocably dead, he still had a chance to live if one performed the simple act of opening the chest and squeezing the heart in the manner repeatedly demonstrated at the Beck course. By such an act, blood pressure could be immediately restored and the patient kept alive as long as massage propelled oxygenated blood to the brain. As Beck had so often stated, "The heart may be just too good to die; give it a chance to reestablish a rhythm and the man will live." In this new approach to cardiac standstill respiratory and cardiac resuscitation fell into their proper places, respiratory resuscitation always preceding and accompanying cardiac massage of the heart, for without oxygen in the propelled blood, massage became merely a gesture, dramatic but useless.

Furthermore, agreement was general that hypoxia of the myocardium sensitized it to the triggering effect of many causes, resulting in standstill and occasionally in fibrillation. In fact, it was admitted that most instances of cardiac standstill could be averted if hypoxia were prevented. This sweeping conclusion explains why so much space has been devoted in this section of Cardiac Resuscitation to the respiratory factor.

The April course in respiro-cardiac resuscitation brought to an end the regular isolated course in respiratory resuscitation which the N.R.S. had presented so consistently through the years, for it was now apparent that respiratory resuscitation without the necessary climax provided by cardiac resuscitation was an incomplete view of the problem. Competition for attention does not exist here. The fact that the mortality from hypoxia is from 10 to 50 times that of cardiac standstill is not important to the patient requiring cardiac massage. On the other hand, the dramatic appeal of a technically simple, but major surgical procedure, must not overwhelm the essential need for immediate and sustained respiratory support.

Indoctrination Courses in Respiro-Cardiac Resuscitation

The courses in respiro-cardiac resuscitation held in New York City in April and June 1958 were pilot projects. They should be repeated and multiplied over the country. In confirmation of this conviction the program followed is now presented in detail. To assist in the logistics of setting up such a course, the N.R.S. is accepting invitations to present it in metropolitan areas in the United States. It is only by sitting in on such a course and partaking of the clinical procedures that the intangible factor of timing can be realized.

Instruction occupied two full days. It began at 9:00 a.m. on Thursday and went through to 5:00 p.m. Friday. It took place at the New York Academy of Sciences, 2 East 63rd Street, New York City. While the surroundings were beautiful and commodious, offering a darkened hall for meetings and adequate space for demonstrations and surgery, there were no other medical conveniences whatever. This fact may be kept in mind as offering freedom to repeat this course, wherever indicated. One does not require university, medical school, or hospital facilities. As will be noted, however, the logistic details are involved and precise team work must be made to click.

Personnel: The total personnel involved amounted to 12 persons, 4 surgeons, 2 anesthetists, 2 surgical technicians, a truckman, secretary, receptionist, and porter.

Material and Equipment: The clinical material consisted of seven dogs and three cadavers. The attendance was made up of 32 students inincluding guests. Complete equipment was provided for respiratory and cardiac resus-

citation. This included three sets of laryngoscopes and endotracheal tubes and oxygen insufflation equipment for each set, all surgical instruments, drugs and solutions for open chest cardiac surgery, gowns and two sets of gloves for 40 persons, Equipment for electrocardiograms was available complete with oscilloscope, cardiac fibrillator and defibrillator, and anesthetic equipment for open chest surgery. Incidental equipment consisted of a slide projector, sound motion picture projector, a public address system, and tape recording equipment.

Finally, facilities were provided for coffee and sandwiches. One of the students attending remarked, "This must be a very expensive course to operate. I don't see how it can be done on a matriculation fee of 75 dollars!" He was correct. The course was and is costly and the student group included guests. However, it was felt that no expense should be spared. Such a course must be right in every detail. It proved to be, as indicated by tape recordings made on the spot.

Prevention of Cardiac Standstill: The first session took off promptly at 9:00 a.m. with a few words of welcome to the Cleveland surgical team. The program outline was stressed. It was pointed out that the first day would be devoted to the prevention of cardiac standstill by anticipating and treating hypoxia. The intramural and extramural, clinical and pathological etiology of hypoxia was considered in detail. It was observed that the total field could be met through a popularization of gas therapy or pneumatology. The link between intramural and extramural accidents is safe transportation. Suitable ambulance facilities for such transportation were described by slides and motion pictures.

With these basic academic considerations behind, the speaker then launched into the technical aspect of prevention, the elimination of the death zone of the respiratory tract in the anesthetized subject. Anesthetic agents, laryngoscopes, and endotracheal tubes were demonstrated and discussed. As a climax to the technic of prevention, the entire group was divided into three sections and adjourned to the laboratory, where three anesthetized dogs were provided for practice laryngoscopy and intubation. Dr. Flagg was assisted by Dr. Edmund Zabriskie and Dr. J. A. Flagg. At the conclusion of this session, a coffee break occurred in the elegant patio of the Academy.

Treatment of Accidental Hypoxia: The afternoon session began at 1:00 p.m. It was devoted to the treatment of accidental hypoxia. The doctrine of the stages of progressive hypoxia was considered in detail. The parallelism between hypoxia, ether anesthesia, obstructive croup, and electroshock therapy was stressed. Emergency procedures, cricothyroidotomy, tracheotomy, and finally laryngoscopy and intubation were considered in detail supported by sound pictures. Finally, a classification of all resuscitation apparatus was suggested, enabling the student to accurately appraise existing and new gadgets. The class then adjourned to the laboratory where cadavers were made available for each of the three groups. Cadaver practice concluded the first day's session. (Note: In the April course a brief open chest dog demonstration was put on at 1:00 p.m. on the first day. In the June 6–9 course all cardiac work was confined to the second day.)

Open Chest Cardiac Massage: The first step in respiro-cardiac resuscitation having been considered, the class was now well prepared to consider the dramatic and final phase of the course, open chest cardiac massage. The entire morning of the second day was devoted to building up the essential background of cardiac resuscitation, its history, incidence, etiology and management, the physiology of the heart beat, the use of cardiac drugs, and finally the instruments necessary for emergency cardiac resuscitation. Dr. Robert M. Hosler of the Cleveland Clinic opened the session and was later supported by his associate, Dr. David Leighninger.

Following the coffee break, the afternoon session opened with a sound motion picture and comments on cardiac resuscitation. A film showing the effect of hypoxia on the dog's brain was shown. A general question and discussion period was then opened headed by the directors of the respiratory and cardiac teams. In preparation for the clinical session to follow immediately, the technic of cardiac massage was described in detail.

The class adjourned to the surgical laboratory.

Here an anesthetized dog with a widely open chest had been prepared. An electrocardiograph and oscilloscope indicated normal blood pressure and rhythm. Each student thereupon caused the heart to go into fibrillation, the blood pressure dropping to zero. His massage of the heart mechanically restored rhythm and blood pressure. The heart was then defibrillated by a counter shock and normal rhythm was resumed. While two spare dogs remained available, the original dog sustained more than 30 fibrillations and defibrillations, the heart returning to normal rhythm at the end of the series.

Future Presentations

This article concludes the series covering the prevention and treatment of hypoxia—the first step in respiro-cardiac resuscitation. This will be followed by the first article of a second series on Resuscitation of the Heart. Between the present article and the first of the second series will appear an article which will attempt to tie in the respiratory and the cardiac factors by a brief consideration of "Man in Vivo," a three dimensional view of form, function, and timing, in which the vital factor of timing will be featured.

Workmen's Compensation for the Cardiac

Results of Questionnaire on Relation of Exertion to Myocardial Infarction

A QUESTIONNAIRE was recently sent to a number of physicians by the New York State Workmen's Compensation Board on the possible causal relationship of strain and cardiac disability. The results are worthy of recording here. The following were the questions asked and the responses received from 398 internists and cardiologists.

QUESTION 1

"In your opinion, can work to which a man is normally accustomed over a period of years and involving no unusual exertion produce heart disease in the workman?"

Answers: Three hundred and seventy-four (93.9 per cent) said *no* or *no with some exceptions;* 6 (1.5 per cent said *yes;* 1 said *possibly;* and 17 (4.2 per cent) did not answer.

QUESTION 2

"Suppose the case of a 60-year-old workman employed for 20 years on a job that regularly required the lifting of 100 pound weights. During the course of this work as customarily performed, he develops a coronary occlusion with myocardial infarction, while lifting a 100 pound weight. From a medical viewpoint, would you consider the attack to be causally related to the lifting of the weight?"

Answers: One hundred and eight-five (46.6 per cent) said *yes* or *possibly;* 197 (49.5 per cent) said *no;* and 16 (4 per cent) did not answer.

QUESTION 3

"Is it your opinion that a workman who suffered a coronary closure and infarction of the heart must have had a pre-existing coronary arteriosclerosis?"

Answers: Three hundred and seventy-two (93.4 per cent) said *yes;* 25 (6.3 per cent) said *no;* and 1 (0.3 per cent) did not answer.

QUESTION 4

"If a workman during the course of his regular work, and where no unusual physical exertion is present, suffers a heart attack following an incident of emotional disturbance occasioned by a verbal argument with a fellow employe or the reprimand of a superior in connection with his work, from a medical viewpoint would you consider the attack as causally related to the emotional disturbance?"

Answers: Two hundred and seventy (67.7 per cent) said *yes;* 106 (26.6 per cent) said *no;* and 22 (5.5 per cent) did not answer.

QUESTION 5

"Assume that a workman suffered a myocardial infarction, and that it was a compensable injury under the Workmen's Compensation Law. He recovered and was discharged as cured, and then returned to work. A year or more later, not during the course of his employment and not due to any physical exertion, he develops another attack of coronary occlusion with myocardial infarction. In your opinion, would the second attack be causally related to the first?"

Answers: Three hundred and thirty (82.9 per cent) said *no;* 51 (12.9 per cent) said *yes, possibly,* or *probably;* and 17 (4.3 per cent) did not answer.

QUESTION 6

"Suppose the case of a workman who has returned to work after recovering from a causally related myocardial infarction. He has a well-healed scar and is asymptomatic. Would you consider that this workman had a permanent partial disability?"

Answers: One hundred and eighty-three (45.8 per cent) said *yes;* 172 (43.3 per cent) said *no;* 18 (4.6 per cent) said *disability for light or moderate work;* and 25 (6.3 per cent) did not answer.

QUESTION 7

"Assume that a man about 25 years of age begins employment at moderately heavy work and continues in this job for 20 years. At the end of this time, while on the job and without engaging in any unusual exertion or strain, he suffers a coronary occlusion with myocardial infarction. In your opinion, is the heart attack causally related to the employment?"

Answers: Twenty-eight (7.1 per cent) said *yes* or *aggravated* or *possibly;* 353 (88.0 per cent) said *no;* and 17 (4.3 per cent) did not answer.

COMMENT

The diversity of opinions expressed by the various physicians indicates that the replies are not based entirely on purely scientific grounds. They are merely expressions of belief or opinion. In fact, we have no definite scientific evidence to prove or disprove our contentions. Our opinions are based mostly on assumed conditions that occur under strain which may or may not produce structural disease of the heart. No small part is played by the conscious or subconscious desire on the part of the physician to help the cause either of the plaintiff or of the defendant.

Because of the importance of this subject, we anticipate discussing each question separately in future issues of the AMERICAN JOURNAL OF CARDIOLOGY, pointing out some faults in the various questions and presenting the most common physiologic disturbances occurring under strain which may produce structural cardiac changes. This will bring us a little closer to an understanding of the possible relationship between strain and cardiac injury.

LOUIS H. SIGLER, M.D., F.A.C.C.
Chairman, Compensation Committee
American College of Cardiology

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, this Journal or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Auricular Fibrillation and Digitalis

Query: I recently saw two patients with auricular fibrillation with rapid ventricular rate (120–130/-min) of recent origin. There were no signs or symptoms suggestive of either mitral stenosis or hyperthyroidism. Congestive failure was absent in both.

In one patient, aged 54, the fibrillation could be ascribed to arteriosclerotic heart disease. The heart was but slightly enlarged on x-ray examination. In the other patient, aged 32, the fibrillation seemed to be of the "idiopathic variety." The heart size was normal. Despite complete bed rest and full digitalization (in the second patient up to 0.3 mg of digitoxin a day for four weeks) it seemed impossible to reduce the ventricular rate at rest to below 90 per min.

What can be done in such cases to further reduce the heart rate with digitalis? Most textbooks do not treat that particular problem of auricular fibrillation with rapid ventricular rate, resistant to digitalis in the absence of mitral stenosis or hyperthyroidism. Are these cases frequent?

Answer: I assume that the apical rate of 120 to 130 was at rest; if this is true, the reduction of rate to approximately 90 seems a fairly adequate response. It is not uncommon for a person who has recently begun to fibrillate to maintain a rate slightly above normal even with the use of digitalis. In fact, if a patient is fibrillating slowly following recent onset it may indicate some disease of the conduction system. The slowing of heart rate is not proportional to the amount of digitalization necessary and digitalis intoxication can occur with rapid rate since digitalis effect is produced by depression of conduction through the A–V node and the bundle of His. I would wonder whether the second patient mentioned might have had excessive digitoxin. With the above mentioned conditions and full digitalization (i.e., to intoxication) it would seem that further reducing the heart rate with digitalis would not be possible and that an attempt at conversion might be indicated. If the rate of 90 at rest is also present with activity, it would seem that the patient is probably having adequate ventricular filling time. A helpful article in this field is that by Craig *et al.* *J. A. M. A.* 166: 2139, 1958.

E. GREY DIMOND, M.D.
Kansas City, Kansas

Anticoagulants in Pericarditis

Query: Do you feel that anticoagulants increase the risk of hemorrhage in the presence of pericarditis following acute myocardial infarction?

Answer: Several deaths were reported, and one fatality was observed by this consultant, caused by hemopericardium as an effect of anticoagulant therapy in the presence of generalized pericarditis.

Query: Has the postinfarction pericarditis syndrome been seen in patients who did receive anticoagulant therapy, particularly those who were given heparin?

Answer: The postmyocardial infarction syndrome has been observed both in patients treated with anticoagulants and in those not treated. There is apparently no causal relationship between anticoagulant therapy and development of the syndrome.

Book Reviews

Blood Pressure Sounds and Their Meanings by J. E. Malcolm. Thomas, Springfield, Ill., 1957, pp. 93, $2.50.

This small monograph tries to explain the Korotkow sounds which appear during compression of an artery. The author has used an "electronic oscillometer" of new description, connected with an oscilloscope, and submits the pulses of the oscillometric curve to a harmonic analysis.

The dynamic theories of the pulse are discussed. The theory of an aortic "standing wave" is accepted with modifications. The theory of a "systemic arterial resonance" with short "stationary waves" having "nodes" and "antinodes," is advocated.

On the basis of the above therapy, the Korotkow sounds are discussed and interpreted, and the various applications are discussed.

The author is to be congratulated for the extreme clarity of his style and the attempt to simplify a series of complex mathematical problems. The data which he presents should be known to all those interested in problems of arterial dynamics. ALDO A. LUISADA, M.D.

Open-Heart Surgery (Chirurgie à Coeur Ouvert) by Ch. Dubost and Ph. Blondeau. Masson et Cie, Paris, 1957, pp. 320, 3,000 fr.

This book is devoted to the study of the present means of performing drainage and opening of the heart; it is an introduction to exsanguineous heart surgery rather than a treatise on surgical tactics or technic. Hypothermia and extracorporal circulation are considered in turn; the critical study of these two methods is based on the works published by various authors, as well as on the personal experience of the staff of the Surgical Centre Marie–Lannelongue (Paris). The critical study of the technic of refrigeration and the physical changes which it brings about, as well as of the surgical limits, dangers and possibilities of hypothermia, brings into relief the short time (less than eight minutes) available to the surgeon for performing the operation.

The authors prefer extracorporeal circulations, especially total ones (artificial heart-lung systems), in which method they see the future of an accurate and complete intracardiac surgery. The hemodynamic factors, the conditions of oxygenation of the blood and the problems of alteration of the circulating blood are the object of a synthetic study. The various procedures which are considered of value at present are passed in review. Provoked cardiac arrest constitutes a considerable advance; it is often the road to success.

The future will certainly bring substantial improvements simplifying the technics and diminishing the risks, but the fundamental principles of cardiac drainage seem to be established henceforth. This book, which is both accurate and condensed and is enriched with illustrations, is not addressed to cardiovascular surgeons alone but to all those (cardiologists, surgeons, physicians) who wish to know the stages which have led to the present possibilities of intracardiac open-heart surgery. R. HEIM DE BALSAC, M.D.

Essentials of Fluid Balance by D. A. K. Black. Blackwell Scientific Publications, Oxford, England, 1957, pp. 127, $3.75.

This is an excellent book; terse, concise, and communicative. Writing, scientific or otherwise, is the art of communicating thoughts and data intact from one mind to another. Here it is well accomplished. The test of lucidity is whether a statement can be read as meaning anything other than what it intends. This book has the quality of lucidity. The style makes it pleasant, easy reading; the book is sprinkled here and there with nice humor. This reviewer has yet to see any similar effort (and there are over 40 such available) that so closely accomplishes its stated purpose. Dr. Black brings to this work an experience in breadth as well as depth. It will serve well the medical student, intern, house staff, and practitioner as well as teacher and investigator.

The biologic role of water and electrolytes is

considered generally; normal physiology and metabolism of water, sodium, potassium, and hydrogen ion are presented and considered separately, followed by clinical implications. A last chapter constitutes an approach to treatment with broad considerations. Dr. Black wisely writes from the point of view that no two patients with water and electrolyte metabolic abnormalities are the same. Pure syndromes do not actually occur; we discuss them as such for purposes of descriptive communication. There are no numerical signs that guide treatment; it is by comprehension of the pathologic physiology and possible metabolic defects that one can hope to have a good experience in recognizing and managing these problems. An approach to treatment is made; no attempt to define specific treatment of given syndromes is found here. This is good and realistic judgment. The pertinent observation is made that metabolic or enzyme aspects of water and electrolyte metabolism have been only superficially explored, as compared to the much more extensive available data on the osmotic and electrostatic effects of electrolytes and water.

Early in the book it is stated that extracellular ground substance offers no barrier to the passage of ions and small molecules; there is a small but impressive body of evidence that its physical and biochemical characteristics give ground substance potential in binding and release of water and electrolyte.

As in practically all books in this area it is the description of hydrogen ion control that is inadequate. The confused terminology makes communication difficult. In this chapter the central issue, behavior of the hydrogen ion, is placed in a subordinate consideration. Acidosis is defined "as a relative increase in the anion content of the body." This misses the point. Acidosis from whatever origin should be considered primarily as excess production of hydrogen ion being only secondarily associated with an anion. The latter appears as a function of the disease entity specifically involved. It is suggested that Dr. Black is looking at the wrong end of the animal.

At another point it is stated that "depletion of cation in excess of anion" also causes metabolic acidosis. Depletion of cation in excess of anion, it seems to this reviewer, cannot occur in the absence of flying sparks. Alkalosis is defined as a state in which there is a "relative excess of cation or deficit of anion in the body." This suggests that the law of electroneutrality is repealed.

The important relationships between potassium, hydrogen ion, and sodium is well communicated and very usable.

This reviewer was especially pleased with the appendices which consisted of seven short succinct discussions of very commonly occurring physiologic processes with implications as to their bedside application. This is excellent. The book is highly recommended.

JOHN H. BLAND, M.D.

Extracorporeal Circulation, compiled and edited by J. Garrott Allen. Thomas, Springfield, Ill., 1958, pp. 518, $7.50.

This is a verbatim report of a Symposium arranged by the Surgery Study Section of the National Institutes of Health in September 1957. Numerous aspects of the technical and physiologic problems in this difficult, developing field are presented.

The subject matter not only deals with pumps and oxygenators but quite naturally with the physiology of perfusion, the responses of individual organs, and myocardial metabolism.

This volume is of value in defining the investigative trends of those most active in this area of surgical activity. The papers and discussions are naturally more meaningful to those already knowledgeable in this specialty.

Unfortunately, the title is that of a monograph—which this collection of papers is not. In fact, a historical introduction would have been of great value in unifying the subject matter. The technical discussion of the apparatus, particularly the pumps and flowmeters, is unnecessarily amateurish. The reader has an uneasy feeling that the speakers might be embarrassed by questions.

The papers of the University of Minnesota group and those of the Mayo Clinic are of particular interest and value.

LESTER BLUM, M.D.

The Pharmacologic Principles of Medical Practice, 4th edition, by John C. Krantz, Jr. and C. Jelleff Carr. Williams and Wilkins, Baltimore, 1958, pp. 1,313, $14.00.

The fourth edition of *Pharmacologic Principles of Medical Practice* by Krantz and Carr is a thoroughly up-to-date book. Both the official and the better unofficial drugs are discussed. The approach to the drugs and the cross-referencing are greatly improved over the last edition. Where it is possible, the mechanism of drug action is stressed, so that rational therapy can be carried out. Part 6, of special interest to cardiologists and to circulatory physiologists, is entitled, "The Pharmacologic Response of the Heart and Circulation." The chapters of this part of the text deal with general considerations, digitalis, quinidine and procain amide, the response of coronary vessels to drugs, hypertension, blood clotting and the hematopoietic system. Each chapter has a useful list of references, chiefly readily available journals and books published in this country in the past 10 years.

The historical notes add color to the text. Fuchs, Professor of Medicine at Tübingen from 1535 to 1566, gave the name *Digitalis purpurea* to the plant we still use in preparing the drug. His celebrated treatise "*De historia stirpium commentarii insignis,*" was published in Basel in 1542. Our name for the plant, foxglove, is said to have been derived from folksglove, i.e., fairies' glove. According to W. Browne,

> To keep her slender fingers from the sun,
> Pan through the pastures oftentimes has run
> To pluck the speckled fox-gloves from their stem,
> And on those fingers neatly placed them.

The mechanism of action of digitalis and of derived glycosides is treated thoroughly and the therapeutic applications are described. The student will be puzzled by the reference to the successful use of quinidine in conjunction with digitalis on the one hand and the emphasis placed on occasional disastrous results from small doses of quinidine in "the heart poisoned by digitalis."

Chapter 43, *Pharmacologic Agents in Hypertension,* deals incompletely with the factors concerned in the regulation of blood pressure levels. Some cardiologists will not accept the statement that hypertension in man is usually of psychosomatic origin. The coverage of drugs applicable to the treatment of hypertension is fairly thorough, the principal omission noted being the tranquilizing drugs—of value especially in neurogenic hypertension. The statement that the principal disadvantage of sodium nitrite lies in the failure of many hypertensive patients to respond favorably to this chemical (page 949) certainly needs explanation. The principal disadvantage of any of the nitrite group lies in the fact that rapid adaptation to the compound occurs, so that the hypertensive patient treated with one of these compounds soon ceases to experience any lowering of blood pressure after receiving a dose.

This textbook of 1,313 pages is weighty evidence of the productivity of the pharmaceutical industry in this country and of the country's lead in synthesizing and evaluating new drugs. This lead was recognized in the U.S.S.R. "Pharmacology and Toxicology" for July-August 1956. This article (translated by the National Institutes of Health) entitled "Problems Involved in Five-Year Plan for Research in Pharmacology for 1956–60" states that the U.S.S.R. lags behind capitalist states in the discovery of new and effective medicinal substances.

DAVID B. DILL

A Contribution to the Study of Portal Hypertension by Alan H. Hunt. E. & S. Livingstone Ltd., Edinburgh, 1958 (Williams & Wilkins, Baltimore, exclusive U. S. agents), pp. 230, $8.50.

The present report, which analyzes 250 personal cases of portal hypertension, has been written with the purpose of reviewing the clinical material in order to evaluate the newer methods of treatment. The first patient was seen in 1947 and the last to be included in this series was observed in 1956. The follow-up observations ranged from six months to many years. This study indicated that cirrhosis of the liver which develops without known predisposing cause is likely to be mild, whereas cirrhosis due to a specific cause is more often severe or progressive. However, the prognosis depends upon the severity rather than the

type of cirrhosis. The portal pressure was found to be a reliable guide as to the extent of portal hypertension but there were exceptions that were confusing. An estimation of the degree of venous stasis by the use of radioactive sodium or by serial radiography was of great value. Percutaneous transsplenic venography was found to have some disadvantages but, combined with direct portal venography, the findings were quite accurate.

The results of surgery revealed that operations on young children with congenital portal vein obstruction were disappointing. The results of operation in portal hypertension due to cirrhosis have been very satisfactory when portacaval anastomosis has been possible in cases of mild or moderate cirrhosis. Lienorenal anastomosis has been less satisfactory. Splenectomy has been effective occasionally. Proximal gastric resection and transection have succeeded only in cases of mild cirrhosis. The problem of advanced cirrhosis remains largely unsolved, as far as surgery is concerned. These patients account for more than half the cirrhotics and only a few survive with treatment and return to work.

The book outlines clearly the management of patients with portal hypertension throughout the pre- and postoperative period, and selected case histories are presented. The reproductions of the venograms and x-rays studies are excellent. This text is a worthy addition to the library of anyone interested in the subject of portal hypertension.

ROBERT A. NABATOFF, M.D.

Biophysical Principles of Electrocardiography by Robert H. Bayley. Hoeber, New York, 1958, pp. 237, $8.00.

In this volume, Dr. Bayley has described the laws that define the flow of currents in volume conductors, the potential distribution that is produced by a field of injury, and an integrative method of analysis of the accession and regression processes relating to the spread of a stimulus through heart muscle.

Chapter 1 describes an idealized volume conductor, dipole fields, field determinants, flow paths and equipotentials, and the derivation of unipolar leads. Chapter 2 describes the accession of the cardiac muscle fiber in terms of the process of depolarization. Chapter 3 describes the properties of vectors and triaxial reference systems.

Chapters on the excited electrical state and its regression, with discussion of the mean electrical axis of T, the ventricular gradient, primary and secondary T wave changes, and a general consideration of currents of injury follow.

Biophysical Principles of Electrocardiography is the first of a projected two-volume set. The second volume will be confined to the clinical aspects of the electrocardiogram. However, in this volume, Dr. Bayley has bravely attempted to interpret clinical electrocardiographic patterns of ventricular hypertrophy, bundle branch block, and myocardial injury in terms of the vectorial principles he has described.

It is hoped that future editions will contain a more adequate bibliography.

EMANUEL GOLDBERGER, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Atrial Arrhythmias, Digitalis and Potassium by Bernard Lown and Harold D. Levine, Landsberger Medical Books, New York, 1958, pp. 282, $6.90.

Cholesterol by David Kritchevsky, John Wiley, New York, 1958, pp. 291, $9.75.

An Atlas of Esophageal Motility in Health and Disease by Charles F. Code *et al.*, Thomas, Springfield, Ill., 1958, pp. 134, $8.50.

Circulation: Proceedings of the Harvey Tercentenary Congress, edited by John McMichael, Thomas, Springfield, Ill., 1958, pp. 503, $10.50.

Handbook of Respiration, edited by Dorothy S. Dittmer and Rudolph M. Grebe, Saunders, Philadelphia, 1958, pp. 403, $7.50.

The Management of Emergencies in Thoracic Surgery by John Borrie, Appleton-Century-Crofts, New York, 1958, pp. 340, $10.00.

Atlas d'Electrocardiographie by V. Fattorusso and O. Ritter, Masson et Cie, Paris, 1958, pp. 311, 3,600 fr.

Pathophysiology in Surgery by James D. Hardy, Williams and Wilkins, Baltimore, 1958, pp. 704, $19.00.

Cold Injury, Ground Type by Col. Tom F. Whayne, and Michael E. DeBakey (edited by Col. John B. Coates), Office of the Surgeon General, Department of the Army, Washington, D. C., 1958, pp. 570, $6.25.

College News

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1959 ANNUAL MEETING

The Eighth Annual Meeting of the College will be held on May 25–29, 1959 inclusive at the Benjamin Franklin Hotel, Philadelphia. Dr. Robert P. Glover has been appointed Local Convention Chairman.

Call for Abstracts of Papers

All members of the College are requested to submit or urge their associates to submit 250 word abstracts of original scientific studies in the field of cardiovascular diseases for the Annual Meeting of the College in Philadelphia on May 25–29, 1959. These abstracts are to be mailed to the Chairman of the Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., for consideration by the Program Committee.

Eight papers will be selected for presentation by members of the College at the Annual Meeting. Abstracts must be submitted by February 15, 1959. Your cooperation is essential to our having a good meeting.

Announcements

Symposium on Congenital Heart Disease

December 29-30, 1958

A Symposium on Congenital Heart Disease will be held December 29 and 30, 1958, at the Sheraton-Park Hotel, Washington, D. C., sponsored by the Section of Medicine, American Association for the Advancement of Science, and endorsed by the American Heart Association and the American College of Cardiology.

The symposium has been arranged by Allan Bass, Secretary of the A.A.A.S., and G. K. Moe, Chairman, Section Nm, A.A.A.S., and is supported by a grant from the National Heart Institute, USPHS.

Further information may be obtained by writing Dr. G. K. Moe, State University of New York, Upstate Medical Center, Syracuse, N. Y. The complete program appears below.

Session I—December 29, 1958, 9:30 a.m.

Development of the Heart and the Origins of Congenital Heart Disease

S. R. M. REYNOLDS, Professor of Anatomy, University of Illinois, College of Medicine, presiding

1. Developmental Processes Involved in Cardiogenesis. ALEXANDER BARRY, Associate Professor of Anatomy, University of Michigan Medical School, Ann Arbor, Mich.
2. Fetal Circulatory Homeostasis. S. R. M. REYNOLDS, Professor of Anatomy, University of Illinois College of Medicine, Chicago, Ill.
3. The Foetal and Neonatal Circulation in Relation to Congenital Heart Disease. GEOFFREY DAWES, Nuffield Institute for Medical Research, Oxford, England.
4. Fetal and Neonatal Circulation: Observations in Humans. FORREST H. ADAMS, Professor of Pediatrics, University of California Medical Center, Los Angeles, Calif.
5. Experimental Production of Congenital Cardiac Defects. JAMES G. WILSON, Professor of Anatomy, University of Florida College of Medicine, Gainesville, Fla.
6. Etiologic Factors in Congenital Heart Disease. JOSEF WARKANY, Children's Hospital Research Foundation, Department of Pediatrics, University of Cincinnati, Ohio.

Session II—December 29, 1958, 2:00 p.m.

The Pathologic Physiology of Congenital Heart Disease

LEWIS DEXTER, Assistant Professor of Medicine, Harvard Medical School, presiding

PRESENTATION OF THE THEOBALD SMITH AWARD

1. The Pathologic Anatomy of Congenital Intra- and Extra-Cardiac Shunts. MAURICE LEV, Director, Congenital Heart Disease Research and Training Center, Hektoen Institute, and Professor of Pathology, Northwestern University Medical School, Chicago, Ill.
2. Hemodynamic Alterations Associated with Septal Defects and Aortic-Pulmonary Communications. EARL H. WOOD, Mayo Clinic, Rochester, Minn.
3. The Pathologic Anatomy of Congenital Obstructive Lesions and of Pulmonary Hypertension. JESSE E. EDWARDS, Mayo Clinic, Rochester, Minn.
4. The Response of the Heart to Obstruction of Ventricular Outflow. S. GILBERT BLOUNT, JR., Associate Professor of Medicine, University of Colorado School of Medicine, Denver, Colo.

Session III—December 30, 1958, 9:30 a.m.

The Diagnosis of Congenital Heart Disease

ANDRE COURNAND, Professor of Medicine, Columbia University College of Physicians and Surgeons, presiding

1. Cardiac Catheterization Techniques Using Pressure, Flow, and Oxygen Analysis. LEWIS DEXTER, Peter Bent Brigham Hospital, Boston, Mass.
2. Indicator-Dilution Technics. EARL H. WOOD, Mayo Clinic, Rochester, Minn.
3. The Characterization of Circulatory Shunts with Foreign Gas Technics. EUGENE BRAUNWALD, Chief, Section of Cardiology, Clinic of Surgery, National Heart Institute, Bethesda, Md.
4. Cinecardioangiography in the Diagnosis of Congenital Lesions. F. MASON SONES, JR., Cleveland Clinic, Cleveland, Ohio
5. Intracardiac Phonocardiography in the Diagnosis of Congenital Heart Disease. DAVID LEWIS, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
6. Relative Role of Various Clinical and Hemodynamic Techniques in Diagnosis of Congenital Heart Disease and in Selection for Surgery. HOWARD B. BURCHELL, Mayo Clinic, Rochester, Minn.

Session IV—December 30, 1958, 2:00 p.m.

Surgical Therapy of Congenital Heart Disease

ALFRED BLALOCK, Professor of Surgery, The Johns Hopkins University Medical School, presiding

1. The Surgical Treatment of Pulmonary Valvular Stenosis and Atrial Septal Defect Using Hypothermia. HENRY SWAN, Professor of Surgery, University of Colorado Medical Center, Denver, Colo.
2. Surgical Correction of Septal Defects and Aneurysms of the Sinus of Valsalva. C. WALTON LILLEHEI, Department of Surgery, University of Minnesota, Minneapolis, Minn.
3. The Surgical Treatment of Cyanotic Congenital Heart Disease. JOHN W. KIRKLIN, Mayo Clinic, Rochester, Minn.
4. Problems of Extracorporeal Circulation. ROBERT GROSS, Ladd Professor of Children's Surgery, Harvard Medical School, Boston, Mass.
5. Present Status and Future Trends in the Surgical Therapy of Congenital Heart Disease. DENTON COOLEY, Professor of Surgery, Baylor University College of Medicine, Houston, Texas.

First Hahnemann Symposium on Hypertension

The Hahnemann Medical College and Hospital of Philadelphia will hold its first symposium on hypertension December 8–12, 1958, at Town Hall, Philadelphia. Each day (morning and afternoon sessions) will be devoted to an aspect of hypertension. Following are the subjects scheduled:

DECEMBER 8: Pathology and Clinical Aspects of Hypertension

DECEMBER 9: Basic Concepts of the Etiology of Hypertension

DECEMBER 10: Pharmacology of Hypertension and Use of Sympathetic Blocking Agents

DECEMBER 11: The Role of Salt and Diuretics in the Therapy of Hypertension

DECEMBER 12: Panel Discussions:
The Development of an Effective Therapeutic Program
The Effect of Therapy on the Prognosis in Patients with Hypertension
The Surgical Approach to Essential Hypertension

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Symposium on
Atrial Septal Defect

Henry A. Zimmerman, M.D., F.A.C.C., ***Guest Editor***

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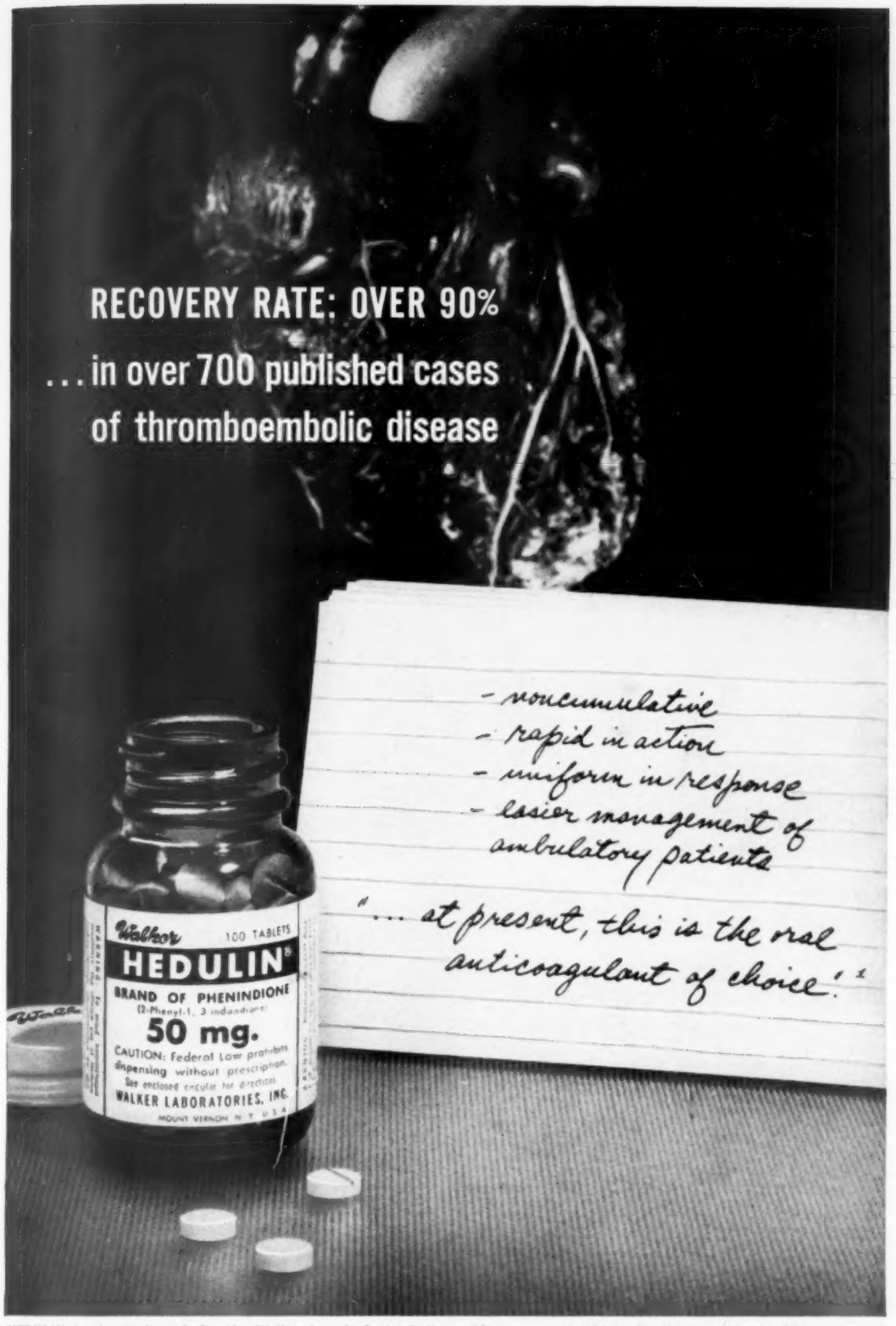

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Volume II DECEMBER 1958 Number 6

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One Year Later . . . . . SIMON DACK 663

Symposium on Atrial Septal Defect

Guest Editor: HENRY A. ZIMMERMAN

Introduction . . . . . HENRY A. ZIMMERMAN 664

Atrial Septal Defects: A Clinicopathologic Appraisal
JOHN S. MACKRELL, JR. AND RAFAEL IBANEZ 665

The highlights of interatrial septal defects are reviewed from the embryologic, anatomic, pathologic and clinical aspects. Six cases of atrial septal defect and one of Lutembacher's syndrome are discussed. Shunting of blood through the defect from the left atrium to the right atrium with resultant increased pulmonary blood flow and right ventricular hypertrophy is the basic physiologic change. Repair in these cases is ordinarily followed by vast improvement in cardiopulmonary hemodynamics. The paucity of autopsy material in this series directly reflects the low mortality rate which has been achieved with definitive surgery utilizing the heart-lung bypass.

Pathologic Physiology of Lutembacher Syndrome
MOHINDER P. SAMBHI AND HENRY A. ZIMMERMAN 681

The etiology, incidence, definition and hemodynamics of atrial septal defect associated with mitral stenosis (Lutembacher syndrome) are discussed. Hemodynamic evidence indicates one lesion may influence the other beneficially. This may account for the occasional case with a long, asymptomatic life span.

Some Physiologic Features of Atrial Septal Defect: Observations in 38 Adult Patients
PAUL WINCHELL AND FOUAD BASHOUR 687

Hemodynamic studies in 38 adult patients with atrial septal defect proved surgically indicate that the left to right shunt in this defect is associated with a marked rise in pulmonary blood flow in the presence of normal systemic blood flow, normal or only mildly elevated pulmonary artery pressure in all but eight cases, decreased total pulmonary vascular resistance and increased right ventricular pressure work. Closure of the defect under hypothermia was followed by reversion of the hemodynamic changes toward or to normal. Of interest was the presence of "relative pulmonic stenosis" with a pulmonary valve gradient of 12 to 28 mm Hg in six cases, which disappeared after surgery. No true pulmonary stenosis was found at operation in one case, suggesting increased volume flow across the valve as the cause for the increased gradient. Also discussed in detail are eight cases with moderate pulmonary hypertension. The causes are not clear but possible factors are vascular changes in the lungs, residual fetal pulmonary hypertension, associated mitral valve disease and pulmonary vascular "spasm."

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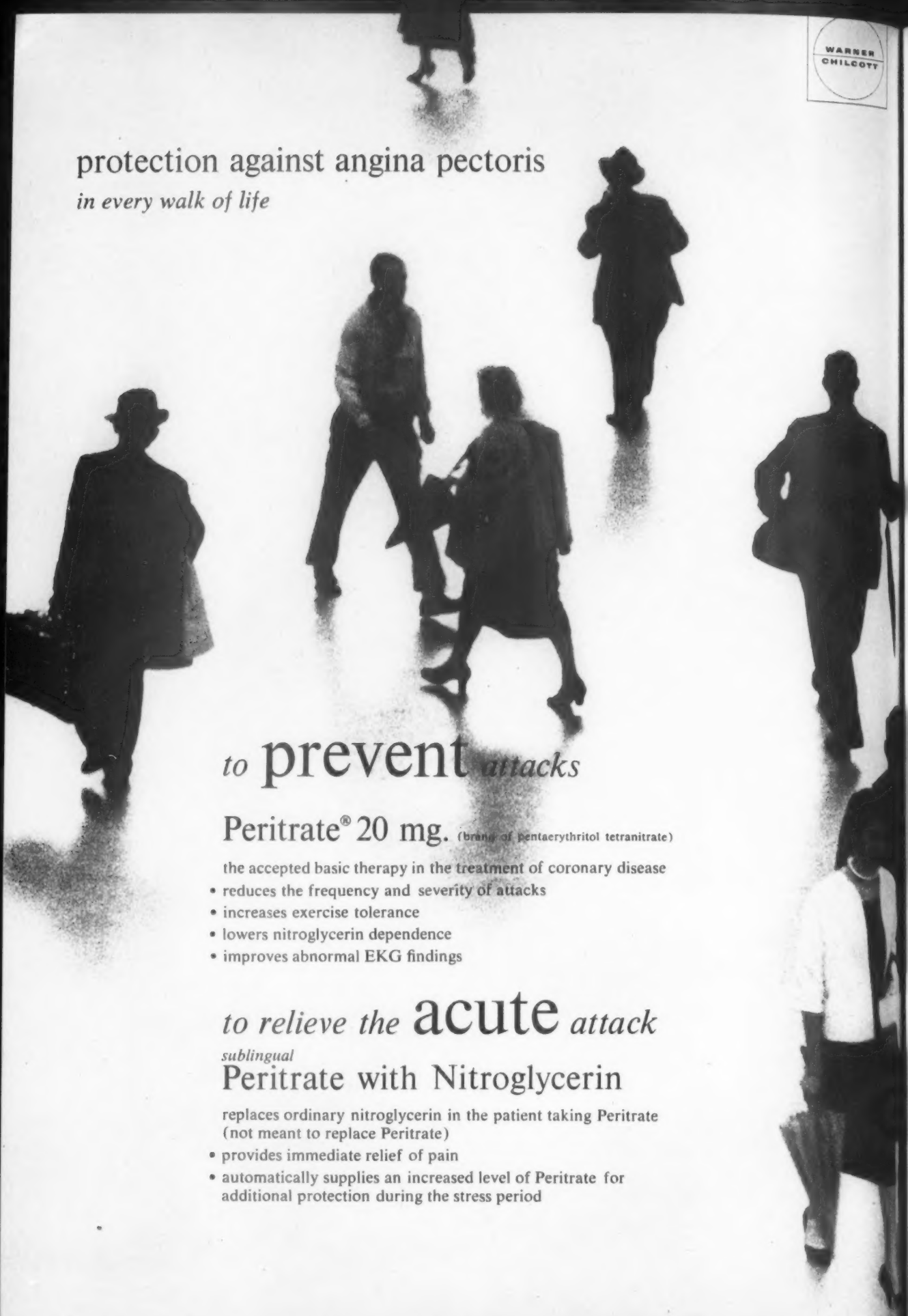

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The Electrocardiogram in Interatrial Septal Defects
JORGE MARTINS DE OLIVEIRA AND HENRY A. ZIMMERMAN 694

This short paper summarizes the electrocardiographic findings in the typical case of atrial septal defect. Although there is no pathognomonic electrocardiogram in this lesion, the diagnosis should be suspected in a patient with congenital heart disease when the following findings are observed: (1) right axis deviation; (2) an R′ or R′s′ pattern in right precordial leads; (3) peaked P waves in V_1 and V_2; (4) absence of signs of left ventricular overloading. The authors believe the R′ pattern in V_1 to be a sign of right ventricular diastolic overloading and evidence of delayed conduction in the basal portion of the right ventricle resulting from dilatation and hypertrophy in this region.

Atrial Septal Defect: The Electrocardiogram and Its Hemodynamic Correlation in 100 Proved Cases
ELY TOSCANO BARBOZA, ROBERT O. BRANDENBURG, AND H. J. C. SWAN 698

The electrocardiographic findings in atrial septal defect are described in detail in this paper. This extensive analysis of the electrocardiograms and hemodynamic data in 100 cases of atrial septal defect proved at operation at the Mayo Clinic discloses no precise quantitative correlation between the electrocardiographic patterns and the hemodynamic conditions. Overloading of the right ventricle as indicated by delay in the intrinsicoid deflection (R′) or increased R/S ratio in V_1 was present in 94 patients, 88 of whom showed electrocardiographic evidence of diastolic overloading. Rather unexpected was the relatively high incidence of overloading of the left ventricle which leads the authors to comment that an additional anatomic anomaly should be suspected in a patient with atrial septal defect who exhibits a prominent Q wave in V_6.

Phonocardiography in Atrial Septal Defect: External and Intracardiac Phonocardiograms
CHI KONG LIU AND ALDO JACONO 714

External and intracardiac phonocardiography has achieved importance not only in interpreting heart sounds and murmurs, but also in explaining their pathogenesis. This comparative study of external and intracardiac phonocardiography, correlated with intracardiac and vascular pressure tracings, demonstrates the site of murmur formation in seven patients with atrial septal defect, clarifies transmission of the murmur from the cardiac chambers to the precordium, and explains the splitting of heart sounds. In left to right interatrial shunt, the splitting of the first sound was due to delayed closure of the mitral valve and delayed opening of the aortic valve. In one case with left to right shunt, a prolonged first sound resulted from the delayed opening of the pulmonic valve. The second sound was usually split because of the delayed closure of the pulmonic valve. The systolic murmurs originated in several locations. In left to right shunt the systolic murmur was maximal in the pulmonary artery and was also recorded in the right ventricle and atrium. A short mid-diastolic murmur seemed to originate in the right ventricle from relative tricuspid stenosis caused by the large flow. A presystolic murmur was usually recorded in several chambers during atrial contraction.

Diagnosis of Septal Defects by the Combined Use of Heart Catheterization and Selective Cinecardioangiography
F. MASON SONES, JR. 724

Heart catheterization combined with selective cinecardioangiography is a useful single diagnostic procedure for the definitive evaluation of congenital heart lesions which is no more hazardous than conventional angiocardiography or right heart catheterization. Examples of technic and results in suspected cases of atrial and ventricular septal defects are presented.

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Surgical Treatment of Atrial Septal Defects: Open Versus Closed Technics
EARLE B. KAY AND HENRY A. ZIMMERMAN 732

A comparison of the operative results in 58 patients with atrial septal defects clearly demonstrates the superiority of the open, direct vision technic performed with the help of a rotating disc pump oxygenator over the closed technics. With the open technic the operative mortality and morbidity were less and postoperative catheterization studies indicated complete closure of the defect.

Seminar on Ballistocardiography (*Part III*)

The Relation of the Ballistocardiogram to Cardiac Function . . . ISAAC STARR 737

The theoretical, the experimental and the clinical approach to the origin and significance of the ballistocardiographic wave form are here detailed. Both the normal and various forms of the abnormal ballistocardiograms seen in the clinic are reproduced experimentally to elucidate the physiologic interpretation of the ballistocardiogram.

Genesis of Displacement of the Human Longitudinal Ballistocardiogram from the Changing Blood Distribution
ABRAHAM NOORDERGRAAF AND CHRIS E. HEYNEKAMP 748

Experimental and theoretical proof is presented in this paper that the ballistocardiogram in great part reflects the circulatory events in the ventricles and larger arteries of the body. Although the authors have omitted their mathematical calculations from their paper, the discussion and the illustrations clarify the interpretation of the force ballistocardiogram in terms of propagation of the pulse wave and changes in filling of the large arteries during the cardiac cycle. The timing, amplitude and direction of the I, J, K, L and M waves are correlated with the rate of change in filling of the thoracic and abdominal aorta and the peripheral arteries. The authors also support the view that the pulmonary circulation makes only a minor contribution to the ballistocardiogram.

Report on Therapy

Infection Complicating Peripheral Arterial Occlusive Disease: Treatment with Intraarterial Histamine and Antibiotics
ISIDOR MUFSON 757

A multidisciplinary regimen based on the repeated intraarterial infusions of antibiotics and the vasodilator histamine is described which has successfully cured infections in limbs with severe arterial obliterative disease. When the occlusion was due to arteriosclerosis, the incidence of success was 85 per cent. Diabetes had no statistical effect on the results. More controversial is the author's poor opinion of the comparative value of other methods. With many references to the literature he argues that the use of homografts and synthetics is experimental, infrequently indicated, technically difficult and its success statistically too uncertain. Permanent improvement is infrequent in the aorta, rare in the thigh, and impossible in the leg. Antigen-antibody reactions destroy the graft and occlude its lumen by thrombosis. Sympathectomy is technically inadequate, its effect being limited to the foot where vasodilation is transitory and quickly reversed. Tolazoline and similar drugs are mild vasodilators, clinically ineffective and a menace to visceral function and life.

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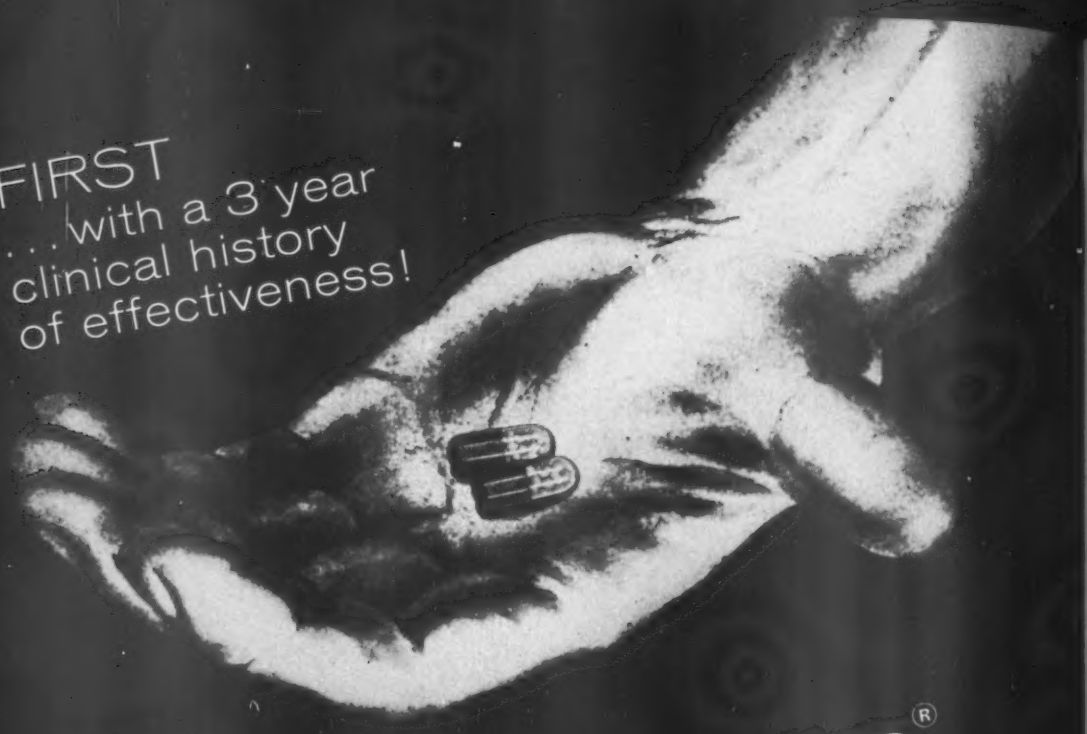

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*Biegeleisen, H. I.; Clinical Medicine; Oct., 1955

*Roberts, J. T.; Clinical Medicine; Nov., 1957

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Historical Milestones

Descriptions of the Endocardium by Bouillaud (1835) and Bichat (1800)
SAUL JARCHO 767

As modern cardiology forges rapidly ahead and numerous articles inundate the medical literature, the basic studies which form the foundation for our advances become lost in obscurity. This month's historical milestone points out that the classical description of the endocardium and the classical statement of its importance in disease date from the 19th century. It is instructive to compare Jean-Baptiste Bouillaud's account (1835) with the vitalistic description of Bichat (1800).

Diagnostic Shelf

Combination of Dextrocardia, Bundle Branch Block, and Myocardial Infarction: Case Report with Vector Analysis of Electrocardiogram
DONALD C. FISCHER 770

Presented here is an interesting combination of electrocardiographic anomalies in the same patient, elucidated by vector analysis of the electrocardiograms.

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Aortic Valve Surgery . . . Mitral Stenosis . . . Coronary Surgery . . . Evaluation of the Transaminase Test . . .

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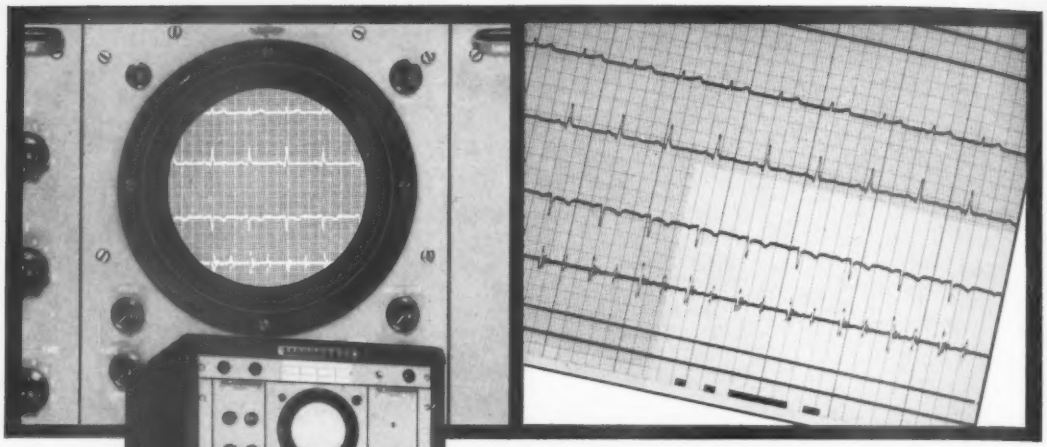

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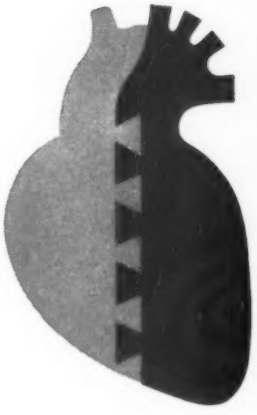
both cause and fear of
ANGINA ATTACKS

proven safety for long-term use



Miltrate*

NEW DOVETAILED THERAPY COMBINES IN ONE TABLET

prolonged relief from anxiety and tension with **MILTOWN®** — The *original* meprobamate, discovered and introduced by Wallace Laboratories

\+

sustained coronary vasodilation with **PETN** — pentaerythritol tetranitrate a leading, long-acting nitrate

"In diagnosis and treatment [of cardiovascular diseases] . . . the physician must deal with both the emotional and physical components of the problem simultaneously."[1]

The addition of Miltown to PETN, as in Miltrate,"...appears to be more effective than [PETN] alone in the control of coronary insufficiency and angina pectoris."[2]

Miltrate is recommended *for prevention* of angina attacks, *not for relief* of acute attacks.

Supplied: Bottles of 50 tablets.

Each tablet contains: 200 mg. Miltown + 10 mg. pentaerythritol tetranitrate.

Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime.

Dosage should be individualized. *For clinical supply and literature, write Dept. 24F*

1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:*395, March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:*504, Dec. 1957.*

WALLACE LABORATORIES, *New Brunswick, N. J.*

CML-7187 *TRADE-MARK

FOR ANGINA PECTORIS
AND INTERMITTENT CLAUDICATION

"DRAMATIC" INCREASE IN BLOOD FLOW[4]

WITH CARTRAX*

PETN (pentaerythritol tetranitrate) and ATARAX® (brand of hydroxyzine)

Relief of pain with PETN, "the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1]

Relief of tension. ATARAX breaks down the pain-fear complex that can trigger an attack—provides added antiarrhythmic[2,3] and nonhypotensive effects.

COMBINED FOR

"more than just a nitrate vasodilating activity."[4] The combination, CARTRAX, increases blood flow "in the larger arteries as well as in the smaller vessels...." Angina patients get greater vasodilation than with one drug alone.

clinical success in 88% of 42 patients "with electrocardiographic evidence of coronary artery disease, all of whom suffered from anginal attacks."[5]

Dosage and Supplied: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." CARTRAX should be taken 30 to 60 minutes before meals, on a continuous dosage schedule. Use PETN preparations with caution in glaucoma. In bottles of 100.

*TRADEMARK

ROERIG NEW YORK 17, N.Y.

DIVISION, CHAS. PFIZER & CO., INC. SCIENCE FOR THE WORLD'S WELL-BEING

1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956. 2. Samuels, S. S.: Angiology *9*:245 (Aug.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol. *1*:624 (May) 1958. 4. Samuels, S. S.: Angiology, in press. 5. Ende, M.: To be published.

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EK-III dual-speed ELECTROCARDIOGRAPH

The new Burdick dual-speed EK-III is not *miniaturized!* Smaller and lighter, it still produces a sharp, full, standard-sized 5 cm. record — at either 25 mm. or 50 mm. per second!

The unit weighs just 22½ pounds (26½ pounds with all accessories). Compact design and unique carrying handle make the EK-III the ideal instrument for accurate office cardiography, as well as for bedside use.

Investigate the advantages of the new Burdick EK-III. Your Burdick representative will gladly demonstrate the instrument at your convenience . . . or write directly to the company for complete descriptive material. No obligation, of course.

Routine electrocardiograms are important under age 40 for future comparison; over age 40 for screening.
JAMA, Mar. 28, 1953

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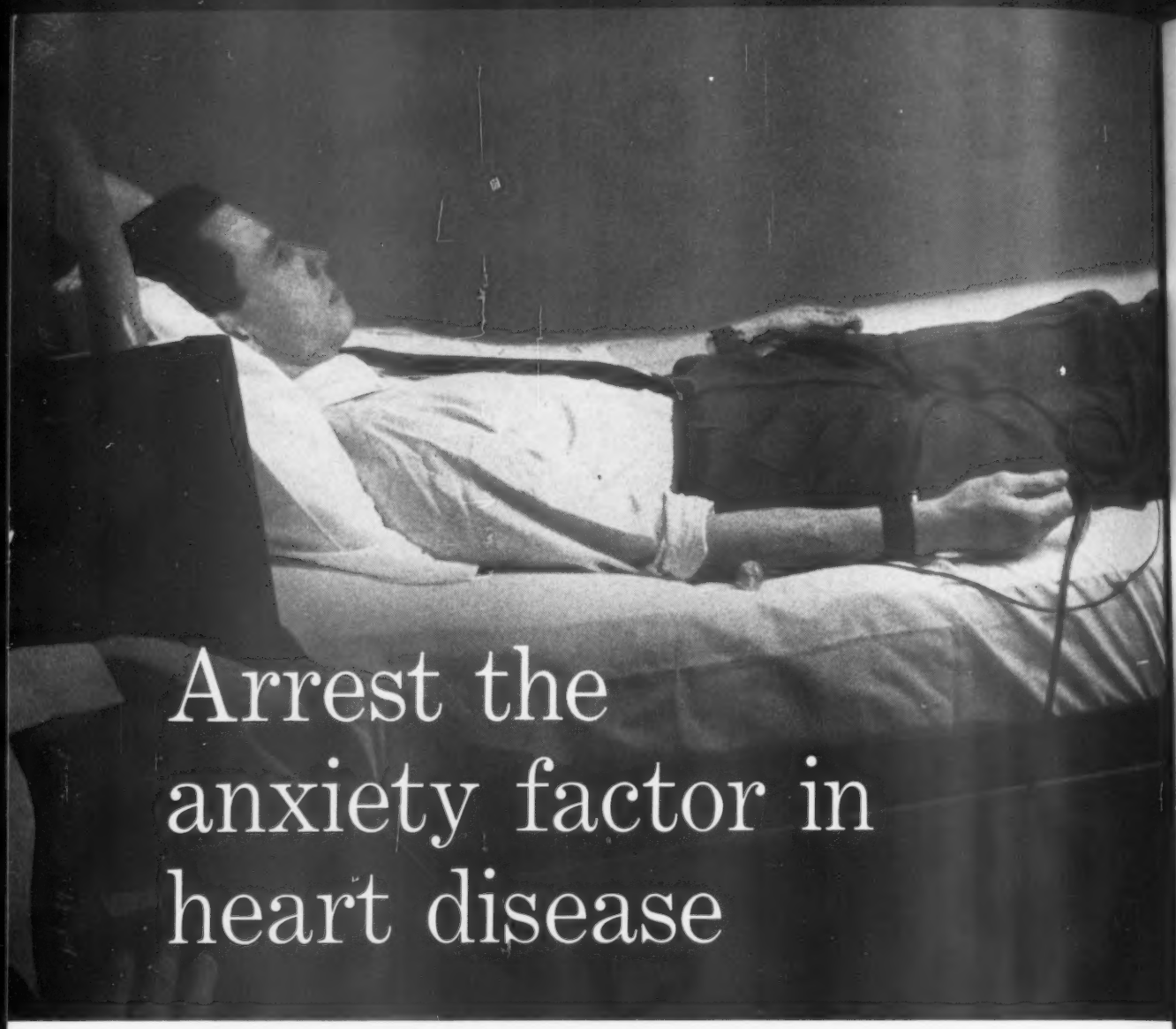

Arrest the anxiety factor in heart disease

without affecting autonomic function

"A cardiac breakdown might be forestalled or arrested" by effective treatment of nervous tension and anxiety.* ■ Adjunctive therapy with meprobamate "definitely reduced nervous tension and anxiety" in all heart patients (80 cases), and enhanced recovery from acute cardiac episodes in many cases.*

**Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.*

Because of its unexcelled safety, *Miltown is well suited for tranquilization of chronic heart patients. It is well tolerated, relatively nontoxic, and produces no blood dyscrasias, liver impairment, parkinsonism, or nasal stuffiness. It does not mask toxicity of other drugs.*

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Now available in the U. S. . . .

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Known in 44 countries for medical instruments of unmatched versatility and performance standards, Schwarzer now makes available to America the F/S Electrocardiograph and F/S Electroencephalograph. Both the ECG and EEG are sold and serviced by The Mark Company.

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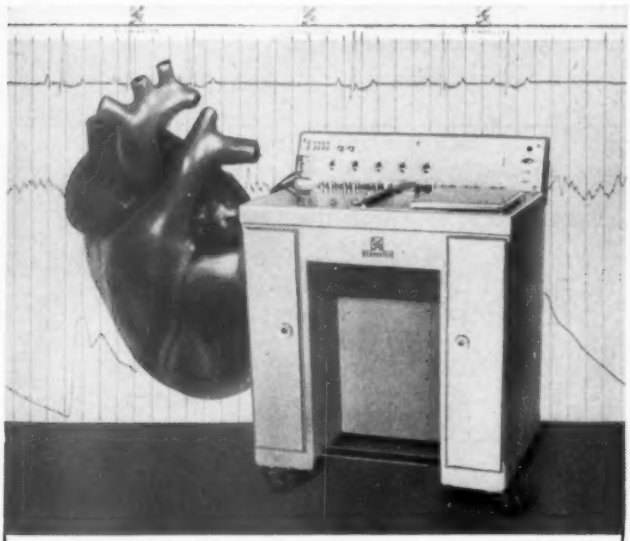

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- Phonocardiographic (detects sounds up to 1500 cps range)
- Recording channels available cover practically entire usable frequency range
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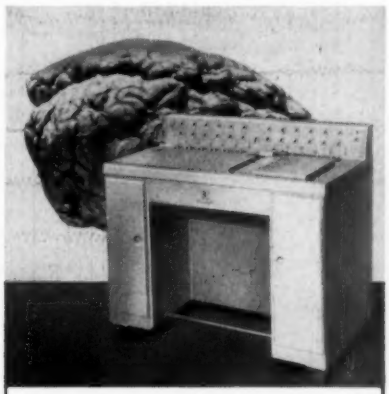
- 1, 4, 8, 12 and 16 channel models. Also available in portable model.



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UNEXCELLED ADVANTAGES...IN BOTH BASIC DIURETIC REGIMENS

DIAMOX*

bicarbonate-regulating diuretic

Acetazolamide Lederle

HOW DIURETICS ACT

Primarily by regulation of bicarbonate transport	DIAMOX acetazolamide
Primarily by regulation of chloride transport	mercurials chlorothiazide

1 **Advantages of DIAMOX in single-drug diuresis**

DIAMOX—operating through the well-understood mechanism of *bicarbonate* transport regulation—provides ample, prolonged diuresis in the great majority of patients.

DIAMOX is virtually nontoxic . . . has not caused renal or gastric irritation . . . has no pronounced effect on blood pressure. It is rapidly excreted, does not accumulate in the body, permits convenient dosage adjustment, allows unbroken sleep. Small, tasteless, easy-to-take tablets . . . usual dosage, only one a day.

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- PREMENSTRUAL TENSION
- EDEMA OF PREGNANCY
- OBESITY

2 **Advantages of DIAMOX in intensive, two-drug diuresis**

When intensive diuresis must be maintained, DIAMOX, alternated with an agent for regulation of *chloride* transport, has proved a regimen of choice. Through dual *bicarbonate-chloride* regulation, it produces maximal sodium-water excretion with minimal distortion of serum electrolyte patterns, greater patient comfort, lessened risk of induced drug resistance.

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Remember this particular patient. He typifies the thousands of patients involved in a clinical investigation which promises to bring about a major change in rauwolfia therapy. The patient is being treated in a Massachusetts hospital. His blood pressure without treatment ranged up to 220/138; now *for the first time,* it is being maintained near normal *without side effects.* This dramatic case history is part of the story of a remarkable new antihypertensive agent **Singoserp**™
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Developed and approved in cooperation with the Medical Profession

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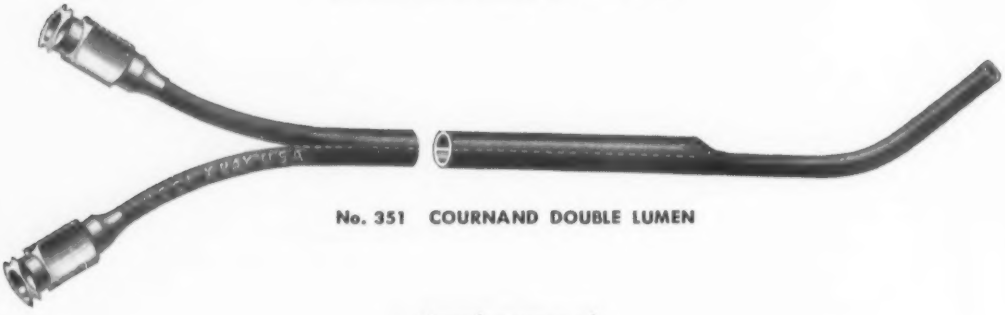

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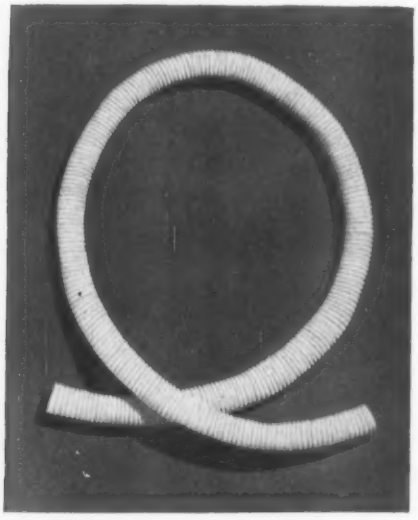

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Glens Falls, New York

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a dosage form

for every type of pain

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5% solution (50 mg. per cc.)
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Ampuls of 1 cc.
Ampuls of 1.5 cc.
Ampuls of 2 cc.
Vials of 30 cc.

10% solution (100 mg. per cc.)
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Vials of 20 cc.
Disposable syringes of 1 cc.

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Ampuls of 2 cc.
Vials of 30 cc.

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Ampuls of 2 cc.

FOR ORAL USE

Tablets of 50 mg.

Tablets of 100 mg.

Elixir, nonalcoholic (50 mg. per 5 cc. teaspoon)
pleasant banana flavor – especially useful for children

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Demerol "in optimal dose . . . is as potent as morphine."
Beecher, H. K. (Harvard University Medical School): *Brit. J. Anesth.* 29:261, June, 1957

1274M

in angina pectoris...
against effort-emotion precipitants

PENTRALINE shields your patient against both the effort and the emotion that can precipitate an angina attack.

The PETN shields him against the effects of *effort*. Safe, long acting and well tolerated, this coronary vasodilator improves the blood flow through the coronary arteries.

The harmful effects of *emotion* are combatted by the other two components of PENTRALINE. Reliable sedative action comes from BUTISOL SODIUM*; and a mild, safe, tranquilizing effect is provided by small doses of reserpine.

Pentaerythritol tetranitrate—10 mg.; BUTISOL SODIUM* butabarbital sodium—10 mg.; Reserpine—0.05 mg.

The usual dose is one tablet four times a day administered *before* meals and at bedtime.

PENTRALINE is not intended for treatment of acute attacks of angina pectoris, but rather for routine daily use as a preventive measure.

*Trade-mark

190A58

McNEIL

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CAMBRIDGE MULTI-CHANNEL RECORDERS

FOR PHYSIOLOGICAL RESEARCH, CARDIAC CATHETERIZATION AND ROUTINE ELECTROCARDIOGRAPHY

Versatile and comprehensive, this series of new multi-channel recorders provides simultaneous indication and recording of EKGs, EEGs, stethograms, peripheral pulse waves, EKYs, BCGs, pneumograms, intra-vascular and intra-cardiac blood pressures, blood pH, dye dilution curves and blood oxygen concentration. Various combinations of these functions can be traced simultaneously on a single record.

Multichannel Photographic Recorder with Monitor

TWO BASIC MODELS ARE AVAILABLE:

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All tracings, Photographic or Direct-Writing are clearcut and accurate. Precise time and amplitude lines insure exact measurements of all tracings. Blood pressure variations, converted to electrical quantities by means of a pressure transducer, may be accurately measured and recorded without use of an external mercury manometer for calibration. The recording of instantaneous and average blood pressures is accomplished directly by operation of a single switch, thus eliminating time taking calculations.

We would be pleased to furnish additional information on the unique features of these fine instruments.

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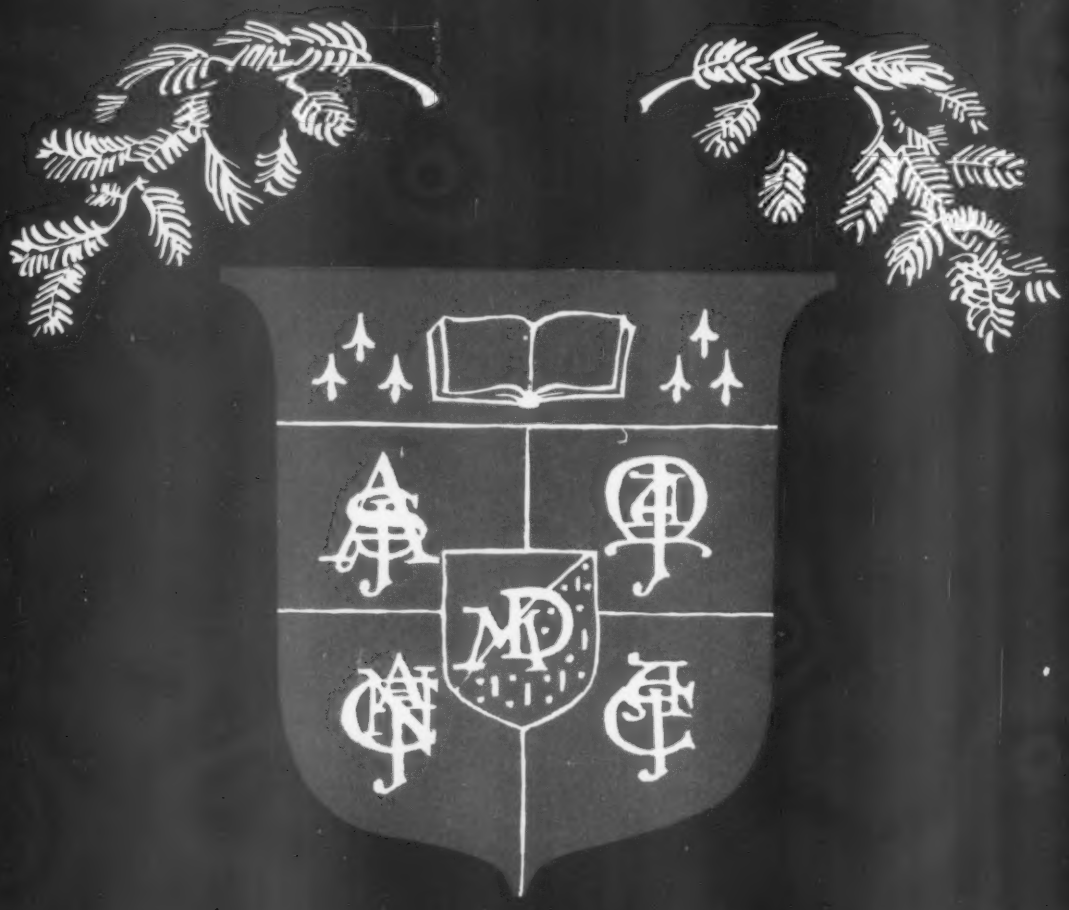
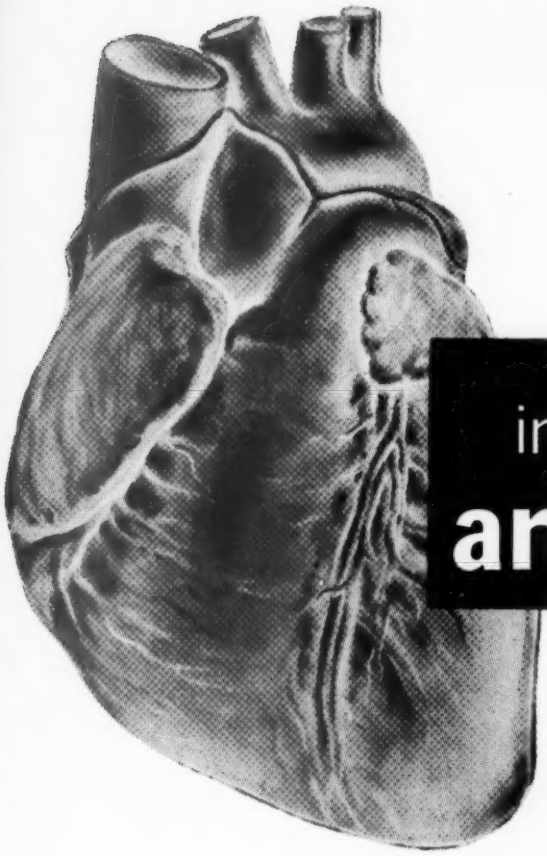


Season's Greetings



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superior
therapy

in **cardiac arrhythmias**

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DURA-TAB S.M.

(Brand of Sustained Medication Quinidine Gluconate, 5 gr.)

INDICATIONS: Premature contractions, auricular tachycardia, flutter, fibrillation.

DOSAGE: **For conversion** of auricular fibrillation to normal rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days. **For maintenance** 1 to 2 tablets every 10 to 12 hours. SUPPLIED: Bottles of 30, 100 and 250.

samples, reprint and detailed literature

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

* Patent Applied For

Successfully treating various arrhythmias with Quinaglute Dura-Tab S.M.®, Bellet and associates[1] cite these major advantages of this long-acting quinidine gluconate*.

- **usually 2 to 3 doses per day — night dose avoided. Each dose maintains plasma levels for from 10 to 12 hours.**
- **elimination of "valleys in plasma concentration" where arrhythmias tend to recur.**
- **a decided reduction of episodes of ectopic rhythm.**
- **better absorption and toleration than quinidine sulfate.**

Pacemaker Model TR-3 shown ⅔ actual size.

NEW MINIATURE CARDIAC PACEMAKER

BATTERY POWERED, ALL-TRANSISTOR CARDIAC PACEMAKER . . . READY FOR INSTANTANEOUS STIMULATION AT ALL TIMES

Another proven ELECTRODYNE instrument developed in conjunction with Paul M. Zoll, M. D. is now available. The all-transistor Pacemaker represents an important addition to the highly specialized line of proven cardiac life-saving instruments now offered by ELECTRODYNE. No time loss, just flip the switch and within three seconds the new TR-3 is delivering stimulation. Operates from one long-life battery or, as an additional feature, may be plugged into any standard AC outlet.

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A built-in compartment holds complete accessories easily available for immediate action.

Open heart surgery: Provision for direct stimulation of heart for treatment of post-operative heart block through a wire attached directly to the myocardium.

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Cardiovascular Disorders

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1. Friedlander, H.S.: Am. J. Cardiol. 1:395 (March) 1958.

Equanil®

Meprobamate

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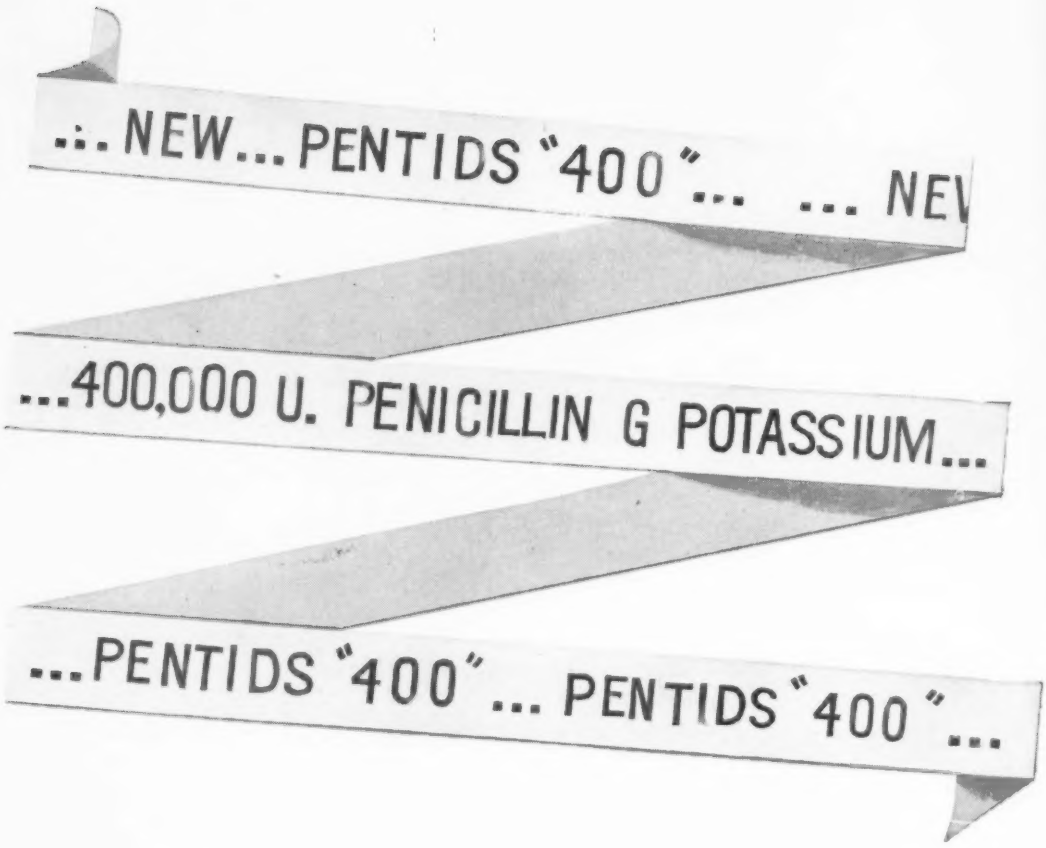
Relieves tension—mental and muscular



New convenient oral tablets . . . PENTIDS "400". . . Economical . . . where double strength Pentids is required for treatment of severe infections due to **Staphylococcus . . . Hemolytic Streptococcus . . . Pneumococcus.** Also indicated for prevention of streptococcal infections when there is a history of rheumatic fever. PENTIDS "400". . . Squibb Penicillin G Potassium 400,000 Unit Tablets (Buffered) . . . Dosage: 1 tablet t.i.d. without regard to meals . . . Supply: Scored tablets—bottles of 12 and 100.

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When anxiety and tension complicate **HIGH BLOOD PRESSURE**

Treatment is more successful when mental pressure and blood pressure are treated together

Miltown

Miltown in addition to ganglionic blocking therapy resulted in subjective and objective improvement in 35 of 37 patients. On the antihypertensive agent alone, only 28 patients improved.[1]

Literature and samples on request

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

The original meprobamate, discovered and introduced by WALLACE LABORATORIES, *New Brunswick, N. J.* CM-6789

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Can be measured . . .

ACCURATELY
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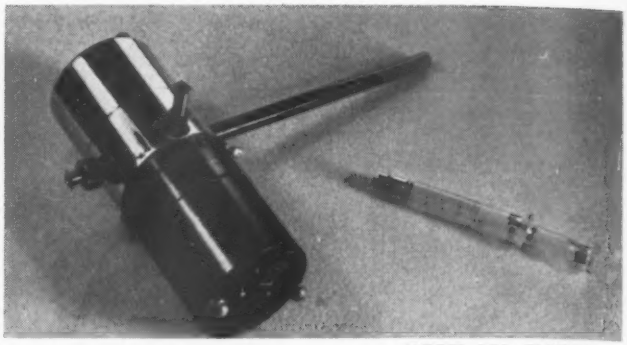

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In angina pectoris

Relax the grip of fear and pain

with COROVAS®
TYMCAPS

Feinblatt,* reporting on COROVAS' disintegration pattern and therapeutic effect in the New England Journal of Medicine, states:

0-3 hours – "During the first hour . . . no significant change in pain level . . . during the second hour most patients experienced a gradual diminution of pain. But at the end of the third hour all patients . . . had significantly less pain."

3-9 hours – "The blood level of (PETN) remained consistently high during this period . . . pain was substantially well controlled. Most of the patients had no pain. . . ."

9-12 hours – "Blood levels continued steady . . . Pain was substantially reduced in all cases and in most cases was completely eliminated."

With your angina patients you will discover – as Feinblatt found – that COROVAS Tymcaps relax the grip of pain and fear . . . all day and all night – day after day.

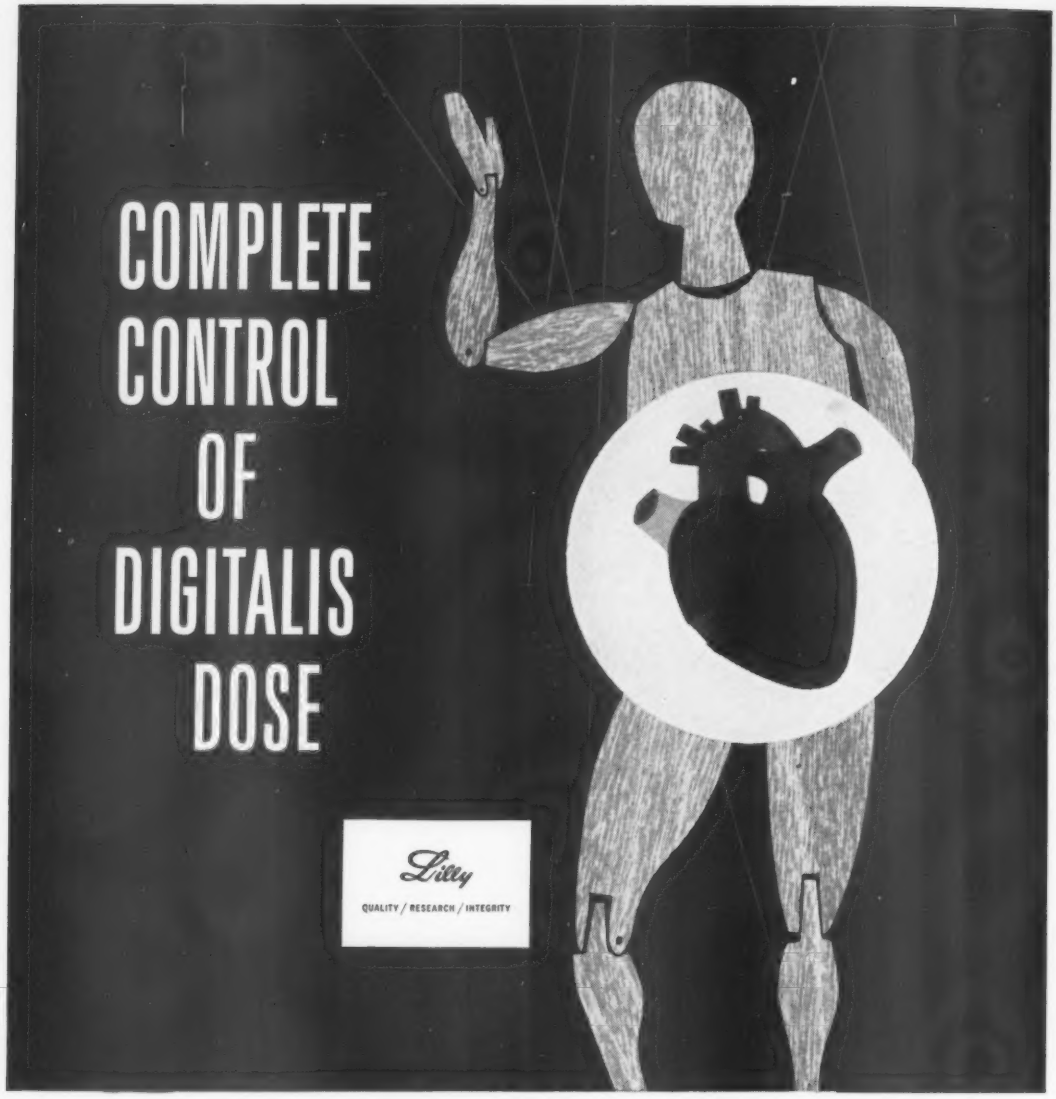
Formula: Each continuous release COROVAS Tymcap contains:
pentaerythritol tetranitrate (PETN) ..... 30 mg.
secobarbituric acid ..... 50 mg.

Dosage: 1 COROVAS Tymcap on arising – 1 COROVAS Tymcap before the evening meal, approximately 12 hours later.

Supply: COROVAS Tymcaps – boxes of 60 and 120.

*Feinblatt, T.M. and Ferguson, E.A.: New Eng. J. of Med. (Feb. 21) 1957.

AMFRE-GRANT, INC. *Brooklyn 26, N. Y.*



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Available in scored tablets of 0.05 mg. (orange), 0.1 mg. (pink), 0.15 mg. (yellow), and 0.2 mg. (white); and in 1-cc. and 10-cc. ampoules, 0.2 mg. per cc.

*'Crystodigin' (Crystalline Digitoxin, Lilly)

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when you treat hypertensive patients

double duty RAUDIXIN

Squibb Standardized Whole Root Rauwolfia Serpentina

is the solid base line for successful therapy

Raudixin helps you relieve pressures in your patients

Raudixin "lowers blood pressure and slows the pulse rate much more efficiently than the barbiturates. . . . It is not habit-forming and is synergistic with all other known hypotensive drugs."*

Raudixin helps you relieve pressures on your patients

Raudixin "relieves anxiety and tension, particularly the tension headache of the mild hypertensive patient, better than any other drug."*

RAUDIXIN..."is the best symptom reliever."*

In mild to moderate cases, Raudixin is frequently sufficient.

Base line therapy with Raudixin permits lower dosage of more toxic agents. The incidence and side effects of these agents are minimized. Diuretics often potentiate the antihypertensive effect of Raudixin.

*Finnerty, F. A. Jr.: New York State J. Med. 57:2957 (Sept. 15) 1957.

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(1) Ridolfo, A. S. & Kohlstaedt, K. G. "A simplified method for the rectal administration of theophylline," to be published.

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*BIBLIOGRAPHY AVAILABLE ON REQUEST.

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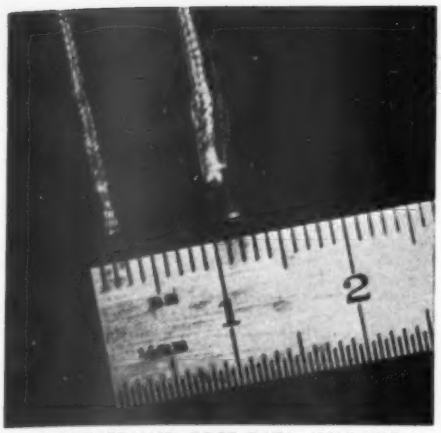

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Riseman, J. E. F., *et al.:* Circulation *17*:22, 1958

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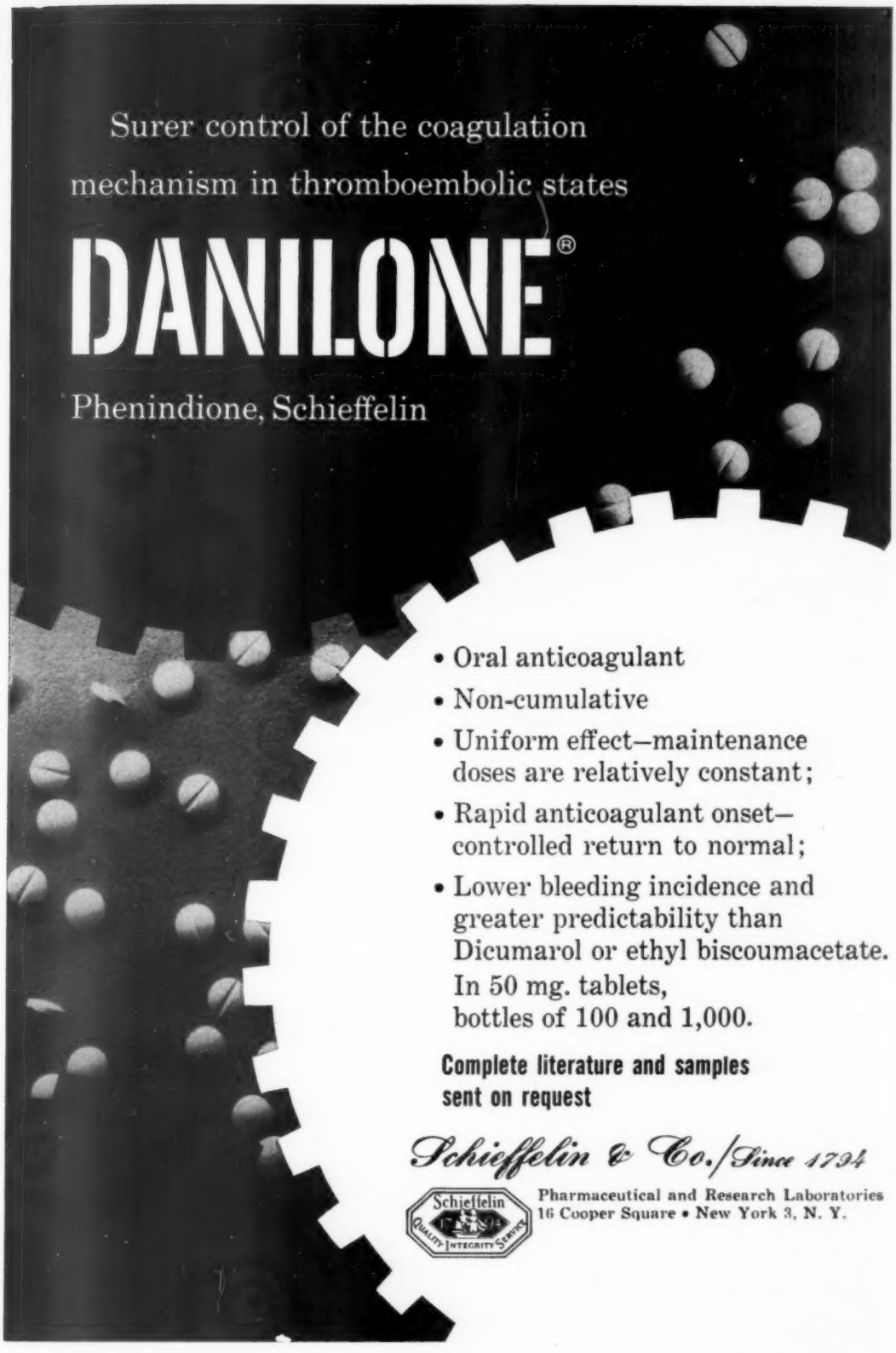

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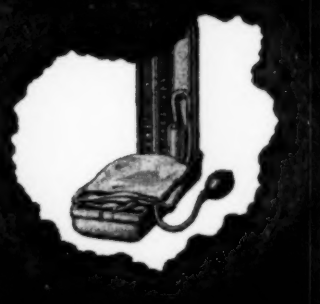
IN HYPERTENSION

Blood Cholesterol Regulation Is Desirable



Patients with hypertension develop atherosclerosis more rapidly and at a younger age than people with normal blood pressure.[1] It is also known that clinical hypercholesteremia is associated with increased atherosclerosis[2] and that many hypertensives show elevated cholesterol levels.[3] For example, in one study including 120 patients with high blood pressure, hypercholesteremia was found in 44% of the hypertensive group.[3]

The consensus of opinion today is that elevated cholesterol levels should be reduced or prevented, and it has been amply demonstrated that this can be done very well by adding linoleic acid and vitamin B_6 to the diet. In scores of patients with hypercholesteremia, and particularly in patients with vascular disease, diets high in linoleic acid produced improvement.[4,5] Vitamin B_6 is apparently necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Thus the body is dependent on an intake of both linoleic acid and vitamin B_6 for normal cholesterol levels.[6,7]

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References 1-7 from the 1956-57 literature supplied on request.

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*Ford, R.V., and Moyer, J.H.: Rauwolfia Toxicity in the Treatment of Hypertension, Postgrad. Med. 23:41 (Jan.) 1958.

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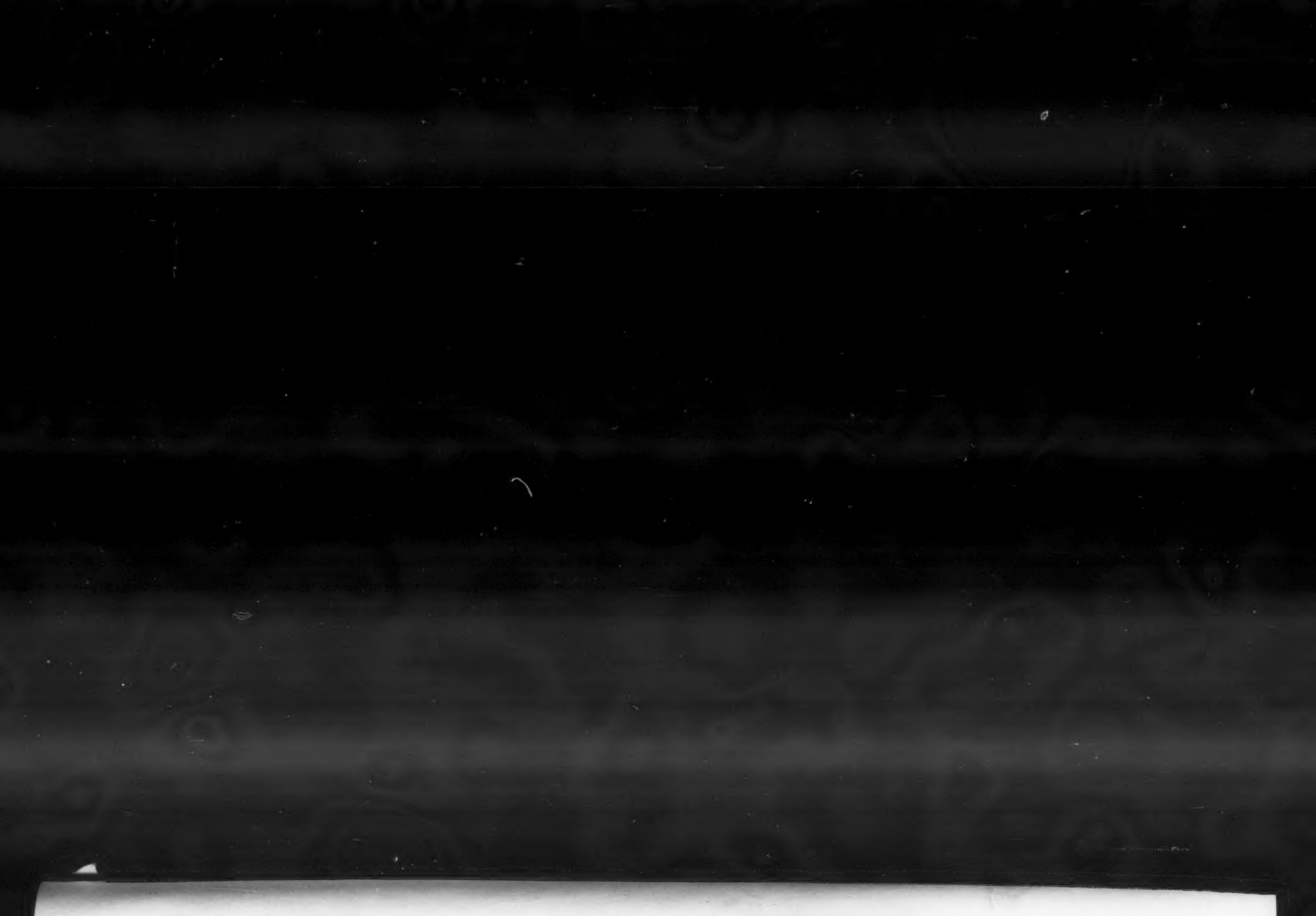
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